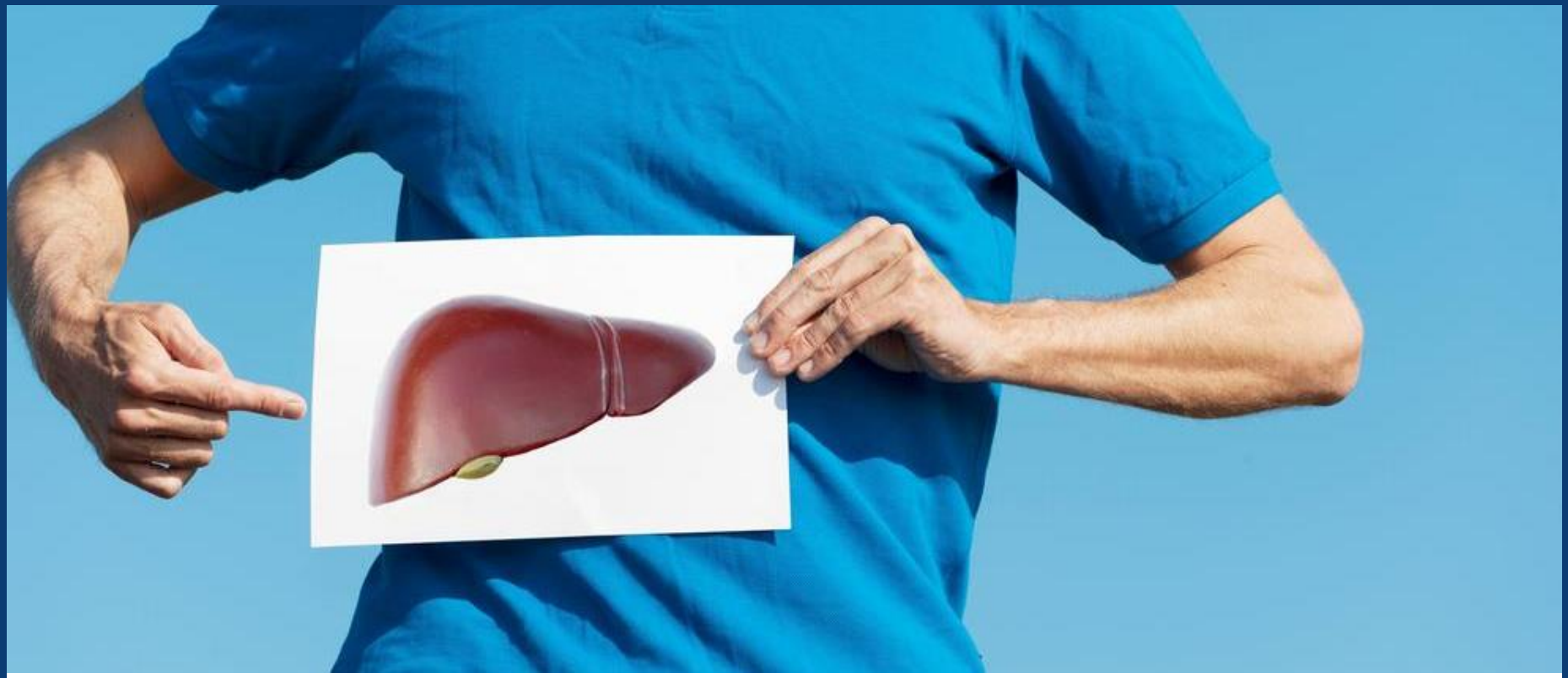


Chronic Liver Disease

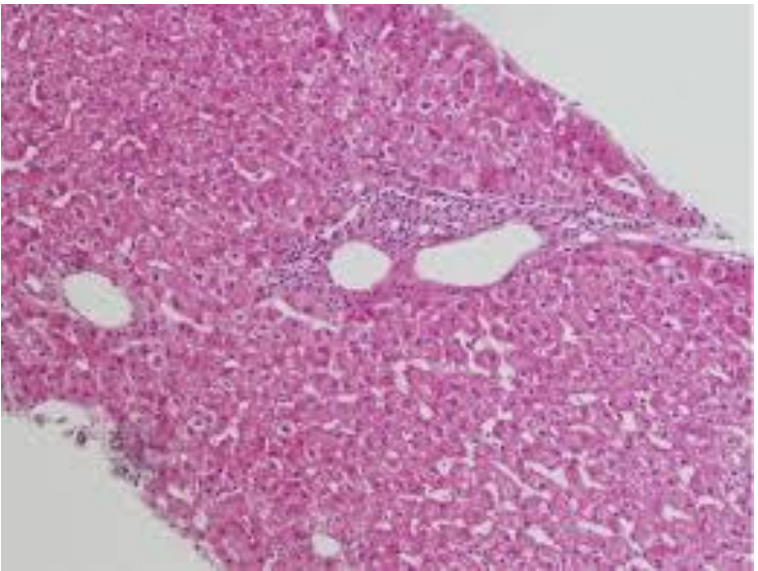
Outline

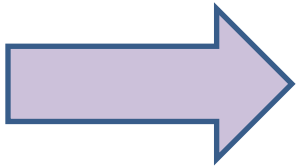
- Causes of CLD
- History, Examination and Investigations for CLD
- Overview of management of CLD
- Overview of acute and Chronic Hepatitis

Liver Cirrhosis

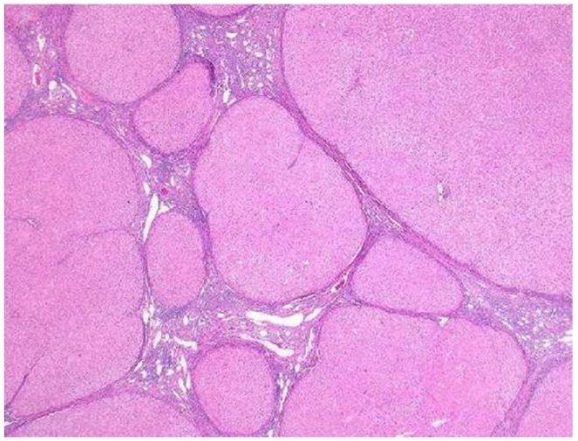
late stage of progressive hepatic fibrosis

- Distortion of the hepatic architecture
- Regenerative nodules





Liver Biopsy – Cirrhosis



Is cirrhosis reversible???

- Irreversible in its advanced stages
- The only treatment may be liver transplantation
- However, reversal of cirrhosis (in its earlier stages) has been documented following treatment of the underlying cause

Causes of cirrhosis

- Chronic viral hepatitis (hepatitis B, C)
- Alcoholic liver disease
- Hemochromatosis
- Nonalcoholic fatty liver disease

Other less common causes

- Autoimmune hepatitis
- Primary and secondary biliary cirrhosis
- Primary sclerosing cholangitis
- Medications
- Wilson disease
- Alpha-1 antitrypsin deficiency
- Celiac disease
- Infection (eg, brucellosis, syphilis, echinococcosis)
- Right-sided heart failure

Clinical Presentation

Compensated

- ❑ Asymptomatic

- ❑ Nonspecific symptoms:
- ✓ Anorexia
- ✓ Weight loss
- ✓ Weakness
- ✓ Fatigue

Decompensated

Jaundice

pruritus

Ascites

Decompensated

Upper GI bleeding

Hematemesis

Melena

Hematochezia

Confusion due to hepatic encephalopathy

Muscle cramps

Diagnosis of liver cirrhosis

(History)

History??

- ❑ Fatigue
- ❑ Easy bruising
- ❑ lower limb edema
- ❑ Fever
- ❑ Weight loss
- ❑ Pruritus
- ❑ Increasing abdominal girth
- ❑ Confusion, sleep disturbances
- ❑ Diarrhea

History of gonadal Problems

Men

- ✓ Impotence
- ✓ Infertility
- ✓ Loss of sexual drive
- ✓ Testicular atrophy

Predominantly in alcoholic cirrhosis and hemochromatosis

Women

- ✓ Amenorrhea
- ✓ Irregular menstrual bleeding

History of underlying cause

- **Hemochromatosis:**
  - Skin pigmentation
  - Diabetes
  - Arthropathy
  - Hypogonadism

- **Autoimmune hepatitis:**
  - Hemolytic anemia
  - Thyroiditis

- **Inflammatory bowel disease (primary sclerosing cholangitis)**
- **Right-sided heart failure (congestive hepatopathy)**
- **Early onset emphysema (alpha-1 antitrypsin deficiency)**

History of exposures??

- ❑ Blood transfusion
- ❑ Illicit drugs
- ❑ Hepatotoxic drugs
- ❑ Occupational or recreational exposure to hepatotoxins (vinyl chloride and mushrooms)
- ❑ Significant alcohol intake

Drug toxicity

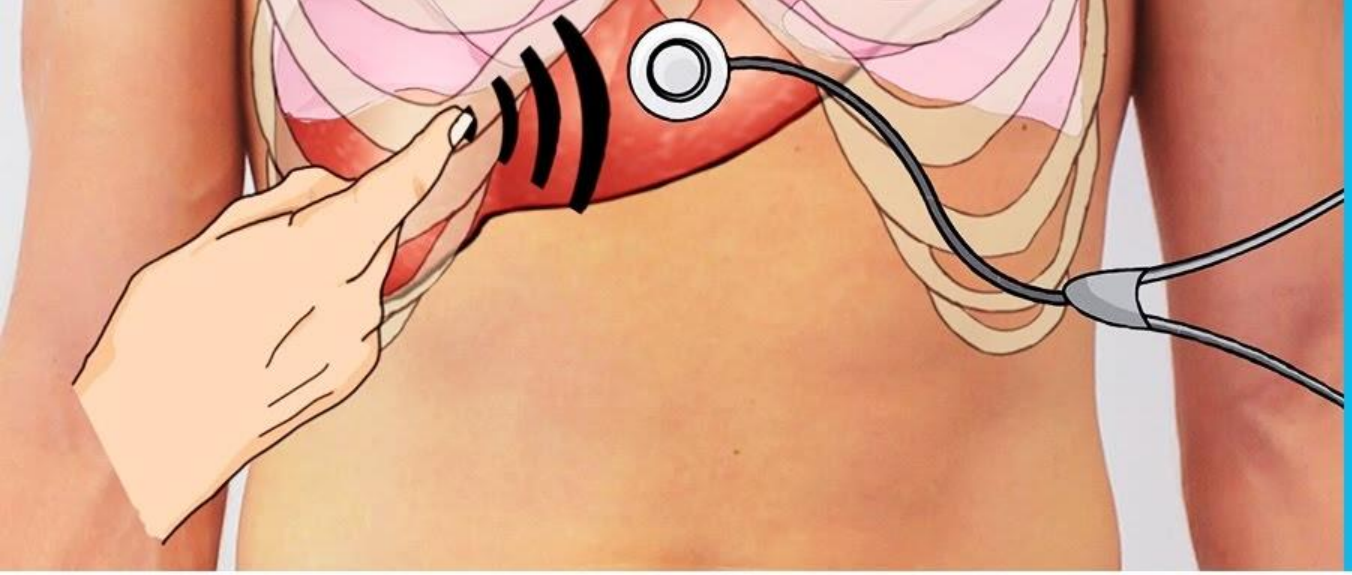
Features that suggest drug toxicity:

- ✓ lack of illness prior to ingesting the drug
- ✓ Clinical illness or biochemical abnormalities developing after beginning the drug
- ✓ Improvement after the drug is withdrawn

If an immunologic reaction is suspected, the illness will generally recur upon reintroduction of the offending substance. However,rechallenge is not advised

Hepatotoxic drugs

- ✓ Acetaminophen
- ✓ Chlorpromazine
- ✓ Valproate
- ✓ Atorvastatin
- ✓ Carvedilol
- ✓ Clarithromycin
- ✓ nitrofurantoin
- ✓ Erythromycin
- ✓ Sertraline
- ✓ Amiodarone
- ✓ Diltiazem
- ✓ Amoxicillin-clavulenic acid
- ✓ Isoniazid



Examination of the liver

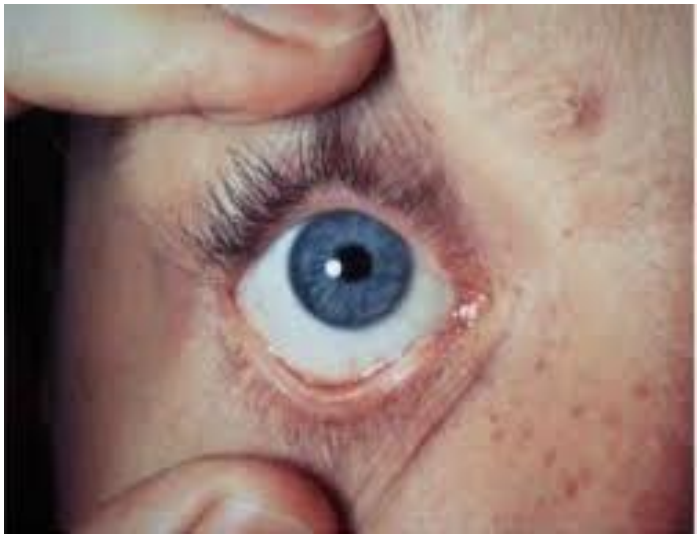
Physical Examination

Decreasing Blood Pressure

- Decrease in mean arterial pressure due to hepatorenal syndrome
- Patients who were previously hypertensive may become normotensive or hypotensive
- An important predictor of survival

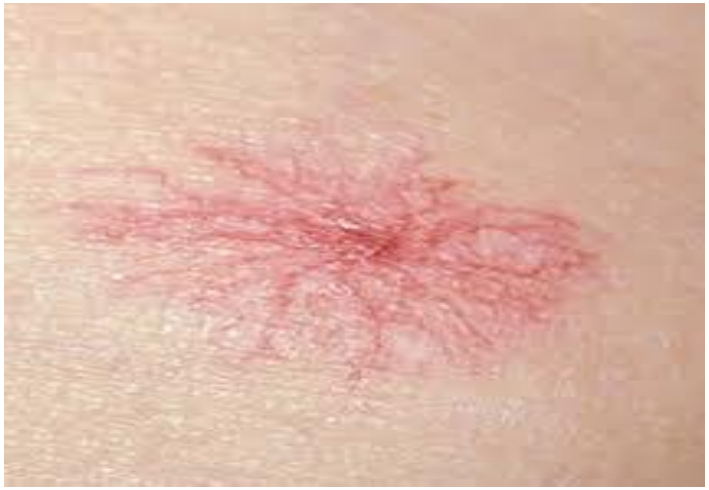
Skin Findings

- **Jaundice**: not detectable until the bilirubin is greater than 2 to 3 mg/dL
- How to differentiate from carotenemia???

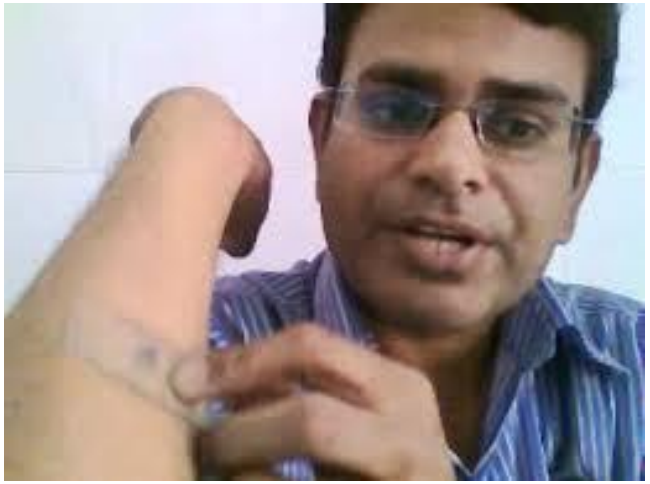


Spider angiomata (spider telangiectasias)

On trunk, face, upper limbs

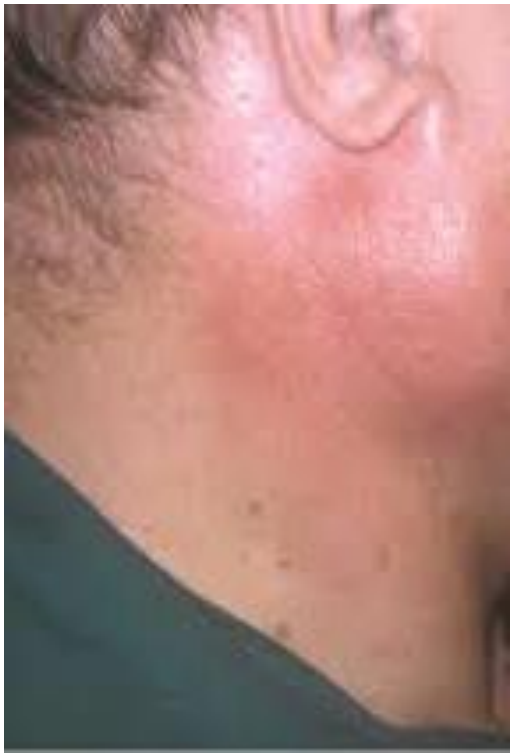


Pulsating when compressed with a glass slide



Not specific for cirrhosis (pregnancy, severe malnutrition)

Head and Neck Findings



- **Fetor hepaticus** due to porto-systemic shunting
- **Temporal and proximal muscle wasting** suggest longstanding disease
- **Parotid gland enlargement**
  - In alcoholic liver disease
  - Due to fatty infiltration, fibrosis and edema

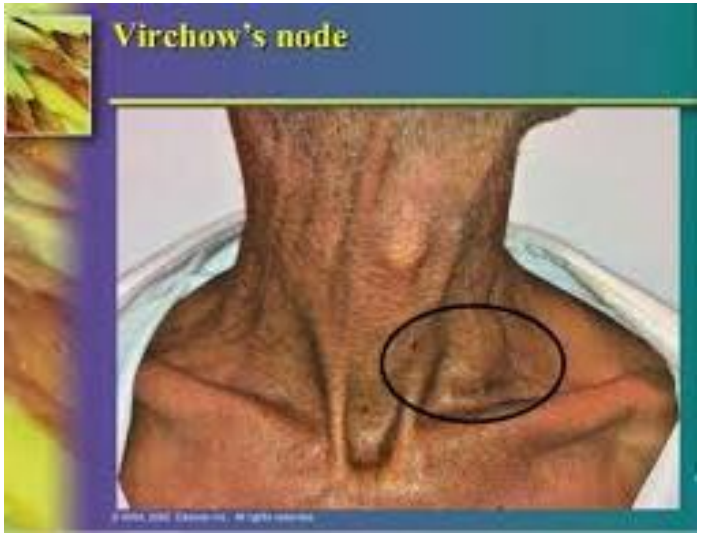
Chest findings

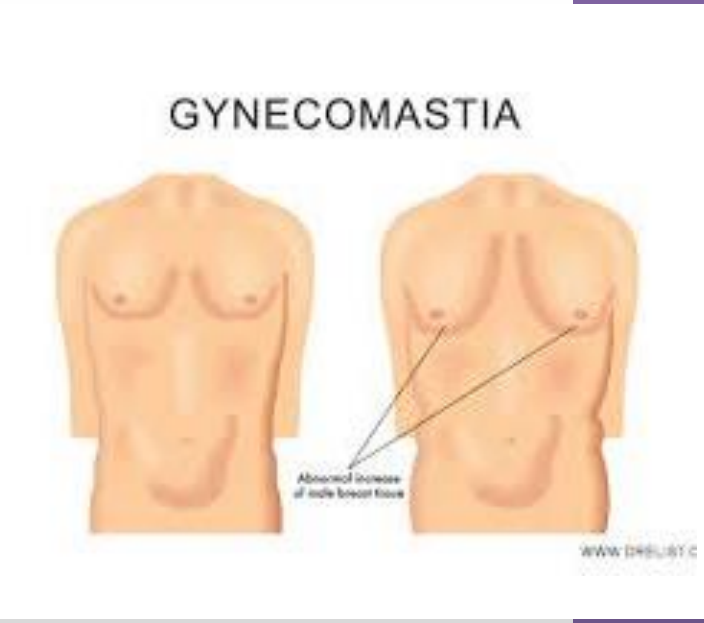
- **Gynecomastia**

In up to 2/3 of patients with cirrhosis

- **Others reflecting feminization**
  - loss of chest or axillary hair
  - Inversion of the normal male pubic hair pattern

- **Virchow's node:** suggest intra abdominal malignancy





Abdominal and genitourinary findings

❑ **Hepatomegaly:**

- Cirrhotic liver may be enlarged, normal sized, or small.
- Palpable liver may indicate liver disease
- Non-palpable liver does not exclude it.

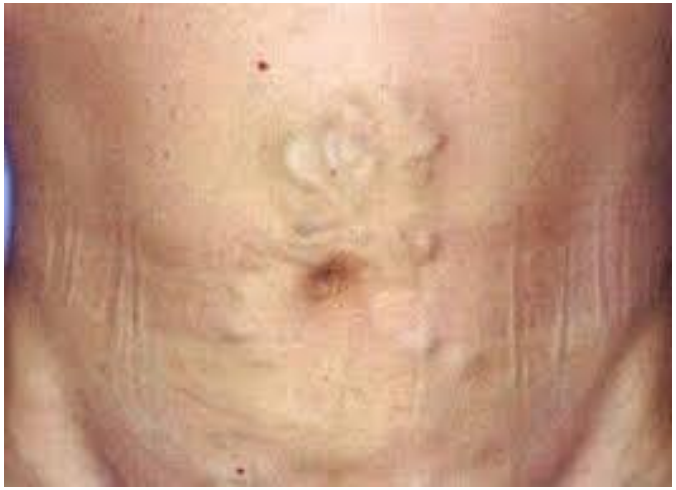
❑ **Splenomegaly:**

- Due to portal hypertension
- Splenic size does not correlate with portal pressures

❑ **Ascites**

Abdominal and Genitourinary Findings

- **Caput medusa:** due to portal hypertension



- **Testicular atrophy**

Cruveilhier-Baumgarten murmur

✓ Venous hum auscultated over the epigastrium

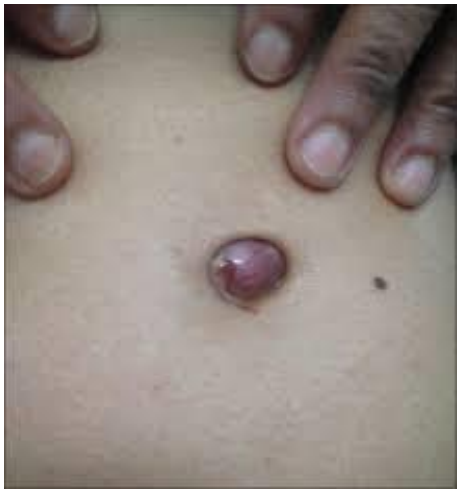
✓ ↑ by valsalva maneuver

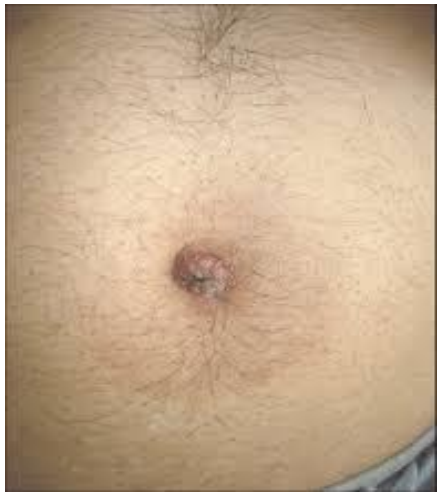
✓ ↓ by applying pressure on the skin above the umbilicus

Sister Mary Joseph's nodule

✓ Periumbilical nodule

✓ Suggest an abdominal malignancy





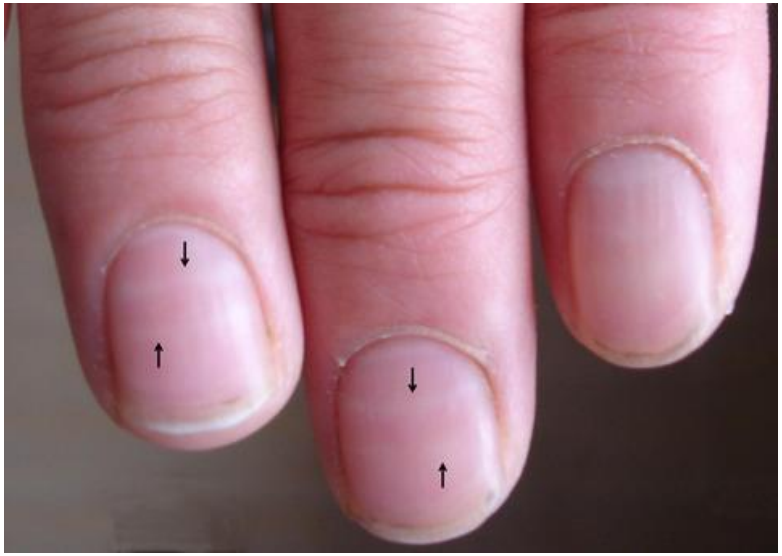
Extremity findings

- **Palmar erythema**

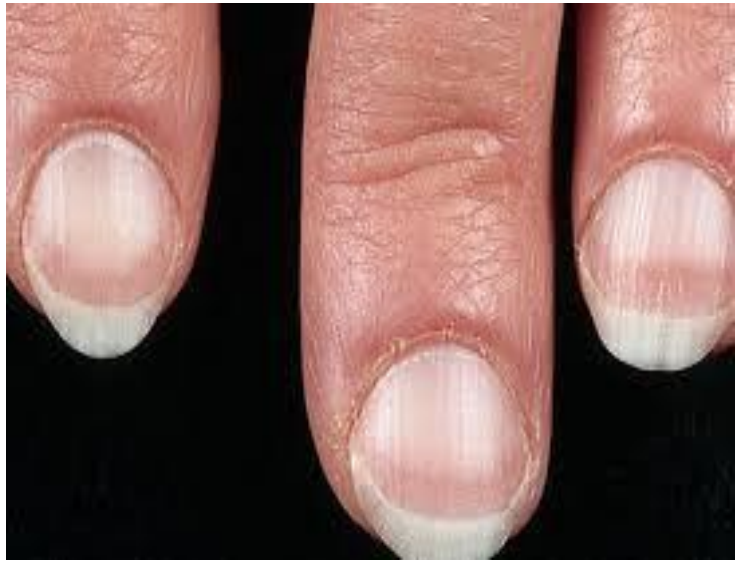
Not specific for liver disease (pregnancy, RA, hyperthyroidism, and hematological malignancies)

Nail changes: caused by hypo-albuminemia

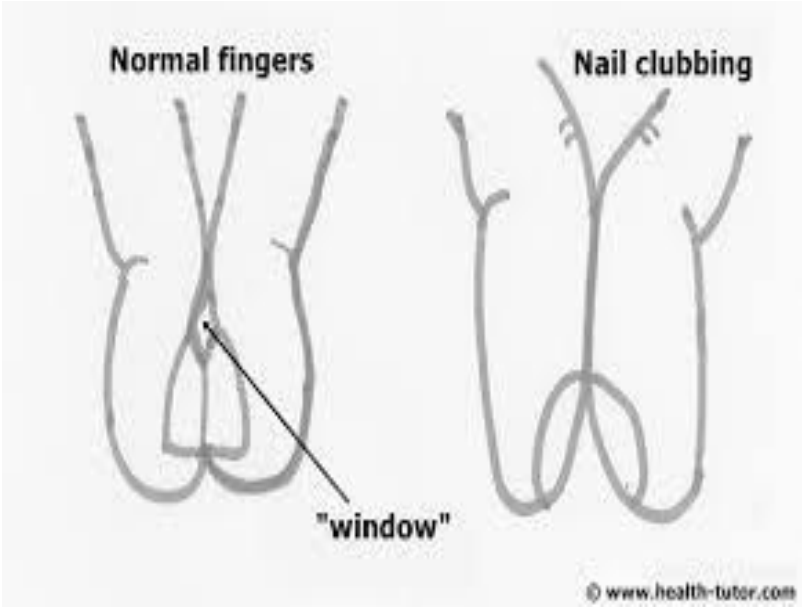
Muehrcke nails



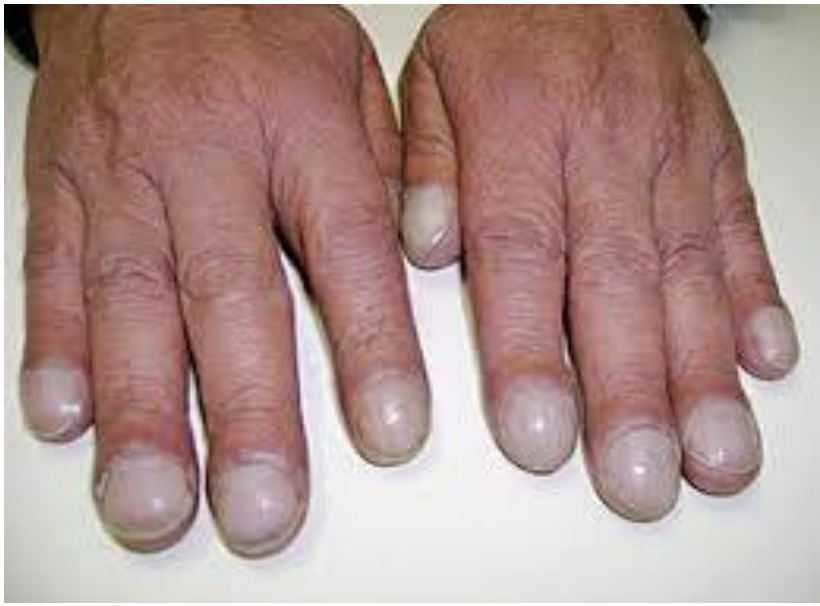
Terry nails



Clubbing

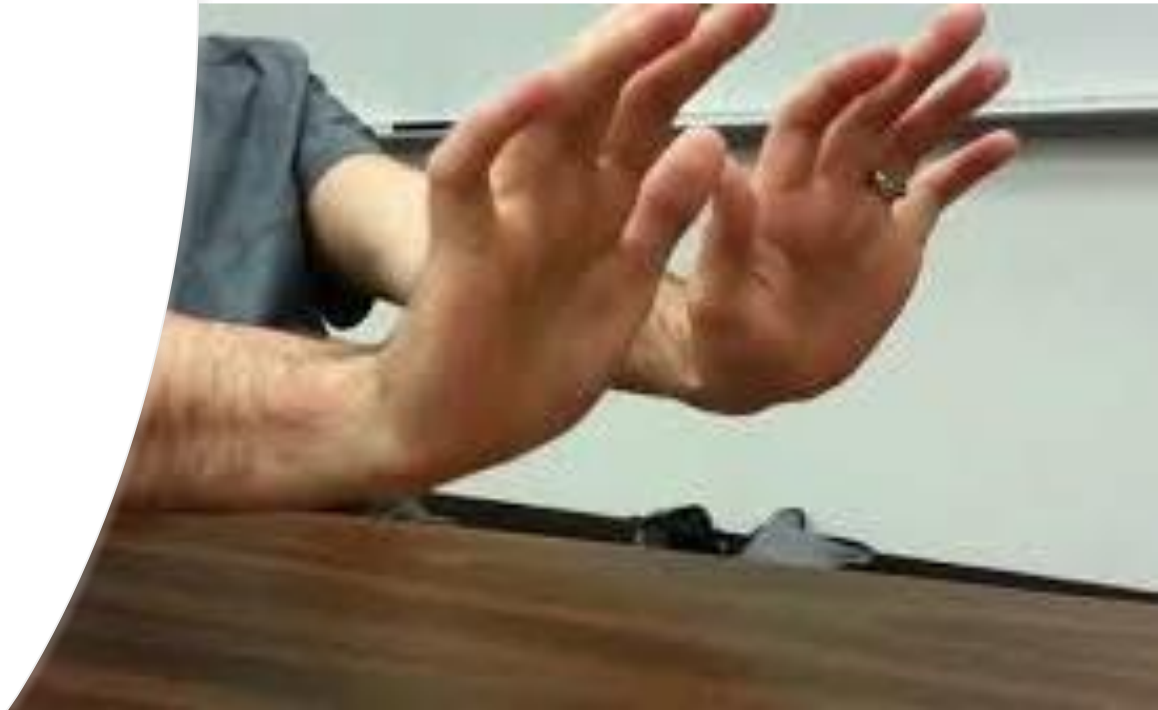


Hypertrophic osteoarthropathy



- **Dupuytren's contracture**

- **Asterixis**
  - With hepatic encephalopathy
  - Also with uremia and severe heart failure



Investigations

Liver Biochemical Tests

Markers of liver injury

- ❑ Alanine aminotransferase (ALT)
- ❑ Aspartate aminotransferase (AST)
- ❑ Alkaline phosphatase
- ❑ Bilirubin

Markers of hepatocellular function

- ❑ Albumin
- ❑ Bilirubin
- ❑ Prothrombin time

Serum Aminotransferases

ALT

- ✓ Present primarily in the liver
- ✓ More specific marker of hepatocellular cell injury.

AST is present in the **liver** and

- ✓ Cardiac muscle
- ✓ Skeletal muscle
- ✓ Kidney
- ✓ Brain

Elevation of liver enzymes

Marked or severe elevations (15 times the upper limit of normal):

- ✓ Acute hepatitis
- ✓ Acute exacerbation of hepatitis B virus on top of underlying chronic liver disease (eg, Wilson)
- ✓ Acetaminophen toxicity

Massive elevations (>10,000 IU/L)

- ✓ Ischemic hepatitis **(>50 times the upper limit)**
- ✓ Drug induced hepatitis.
- ✓ Rhabdomyolysis
- ✓ Heat stroke.

Mildly or moderately elevated aminotransferases

- Chronic viral hepatitis (normal to <2 times the upper limit of normal, rarely > 10 times)
- Hemochromatosis
- Nonalcoholic fatty liver disease (<4 times)
- Alcoholic liver disease (<8 times)
- Autoimmune hepatitis
- Wilson disease

AST to ALT ratio

- **Most causes of hepatocellular injury are associated with ALT higher than AST.**
- **An AST to ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease**

However, the AST to ALT ratio is occasionally elevated in an alcoholic pattern in:

- ✓ Nonalcoholic steatohepatitis
- ✓ Cirrhosis due to viral hepatitis or Wilson disease

Although the ratio typically is not greater than two

Chronically elevated aminotransferases

- ❑ Asymptomatic patients
- ❑ Negative viral, metabolic, and autoimmune markers
- ❑ No chronic liver condition identified by noninvasive testing
- ❑ **Aminotransferases:**

(< twice the upper normal limit)

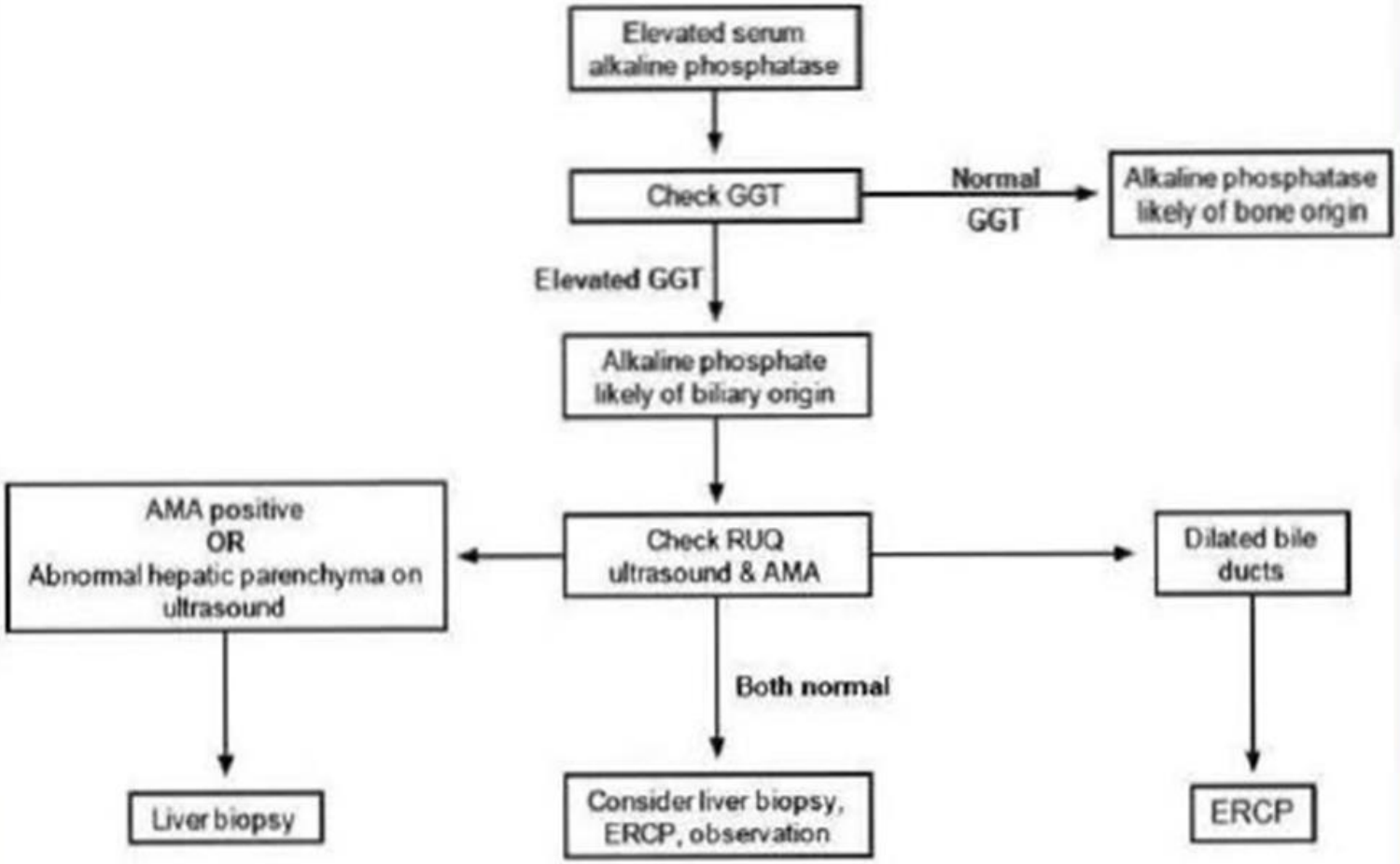
Follow up liver biochemical and function tests every 6 months

(> twice the upper normal limit): liver biopsy

Alkaline phosphatase elevation

- ❑ Liver disease
- ❑ Third trimester of pregnancy
- ❑ Blood types O and B after eating a fatty meal
- ❑ Infants and toddlers
- ❑ DM
- ❑ Benign familial occurrence

Evaluation of elevated alkaline phosphatase



AMA = antimitochondrial antibody; **ERCP** = endoscopic retrograde cholangiopancreatogram; **GGT** = gamma-glutamyltransferase; **RUQ** = right upper quadrant.

Liver diseases??

- **Extrahepatic causes**
- ✓ Bile duct stones
- ✓ Primary sclerosing cholangitis
- ✓ Malignant biliary obstruction

- **Intrahepatic causes**
- ✓ PBC
- ✓ Primary sclerosing cholangitis (antimitochondrial antibodies (AMA), antinuclear antibody, and antismooth muscle antibody)
- ✓ Infiltrative disease (sarcoidosis, amyloidosis)
- ✓ Viral hepatitis
- ✓ Cholestasis of pregnancy

If both the serum aminotransferases and alkaline phosphatase are elevated

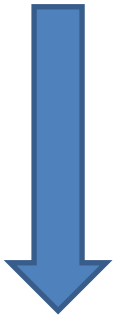
Hepatocellular pattern: disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase

Cholestatic pattern: disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases

The alkaline phosphatase is typically elevated to at least 4 times the upper limit of normal.

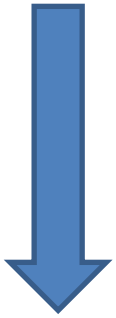
Albumin

Low albumin



Chronic process

Normal albumin



Acute process

Prothrombin Time

Prolonged due to:

- ✓ **Vitamin K deficiency due to prolonged jaundice and intestinal malabsorption of vitamin K**
- ✓ **Significant hepatocellular dysfunction**

The failure of the PT to correct with parenteral administration of vitamin K suggests severe hepatocellular injury

Billirubin

Serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions

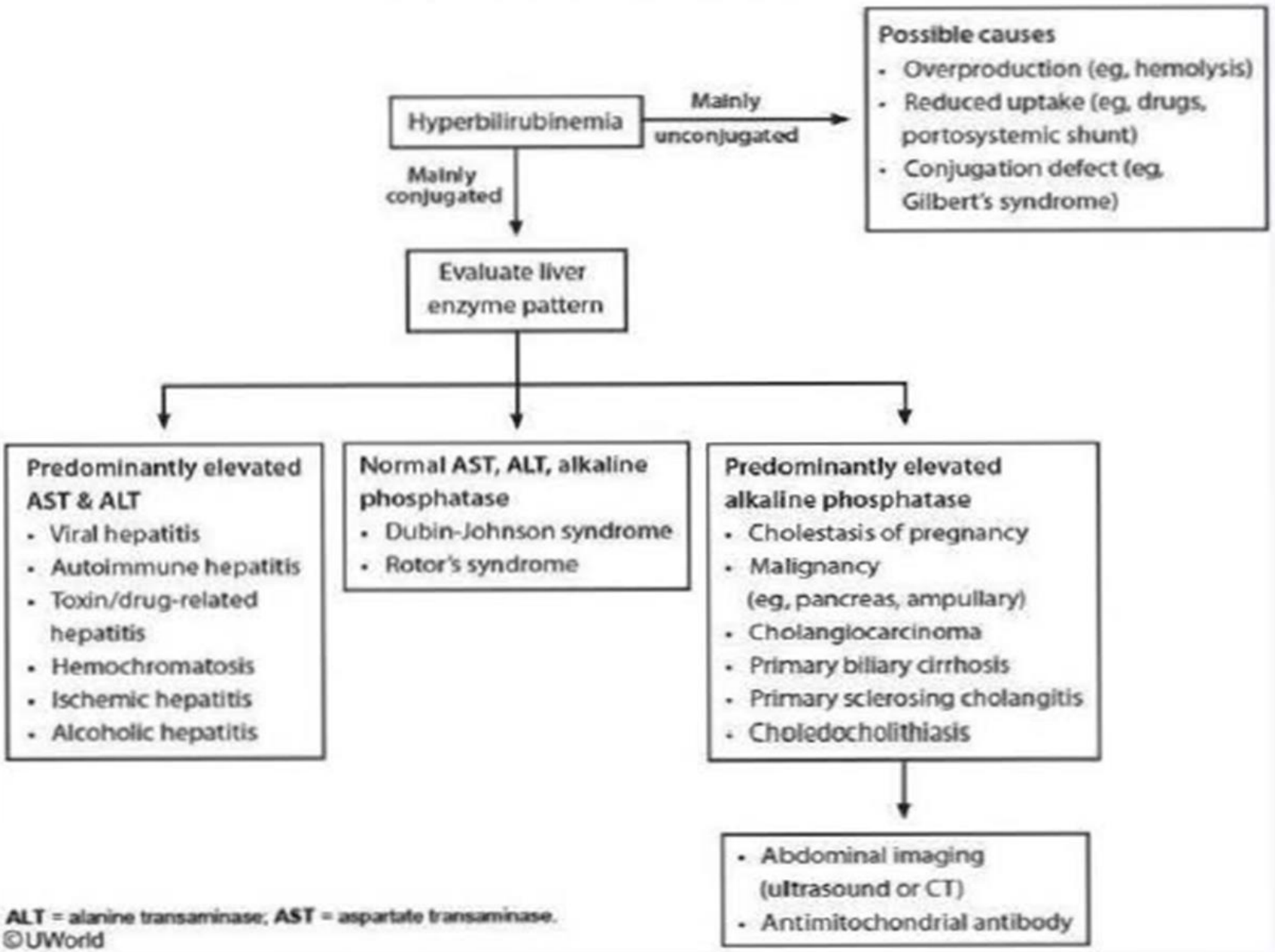
An increase in conjugated bilirubin (direct hyperbilirubinemia):

- Decreased excretion into the bile ductules (Dubin-Johnson syndrome)
- leakage of the pigment from hepatocytes into serum
- defective hepatic reuptake of bilirubin by hepatocytes (Rotor syndrome)

An increase in unconjugated bilirubin (indirect hyperbilirubinemia)

- Overproduction hemolysis
- Impairment of uptake
- Impaired conjugation (Gilbert disease, Crigler-Najjar syndrome, and certain drugs).

Approach to hyperbilirubinemia in adults



ALT = alanine transaminase; **AST** = aspartate transaminase.

Gilbert syndrome	
Epidemiology	• More common in males • Most common inherited disorder of bilirubin glucuronidation
Pathogenesis	• AR or AD mutation in *UGT1A1* gene • ↓ UDP-glucuronosyltransferase activity → ↑ **unconjugated bilirubin**
Clinical findings	• Intermittent episodes of mild **jaundice** • Provoked by **stress** (eg, infection, fasting, vigorous exercise, surgery)
Diagnosis	• Unconjugated hyperbilirubinemia on repeat testing • Normal CBC, blood smear, reticulocyte count • **Normal** AST, ALT, alkaline phosphatase
Treatment	• No specific treatment

AD = autosomal dominant; **ALT** = alanine aminotransferase; **AR** = autosomal recessive; **AST** = aspartate aminotransferase; **CBC** = complete blood count; *UGT1A1* = UDP glucuronosyltransferase family 1 member A1.

Imaging

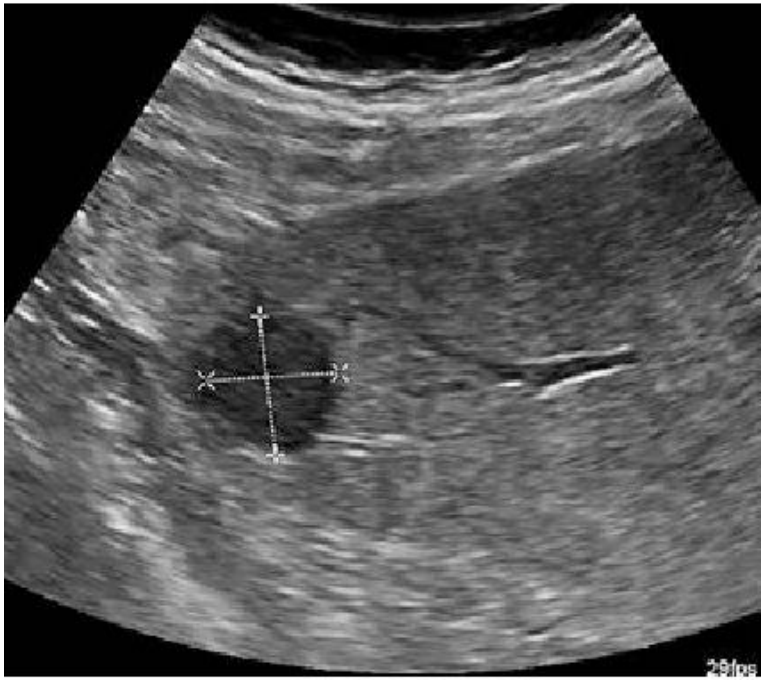
Abdominal ultrasound is typically the first radiologic study obtained

Provides information about:

- ✓ Appearance of the liver
- ✓ Blood flow within the portal circulation
- ✓ Hepatocellular carcinoma
- ✓ Ascites
- ✓ Varices
- ✓ Splenomegaly
- ✓ Hepatic or portal vein thrombosis

Abdominal ultrasound

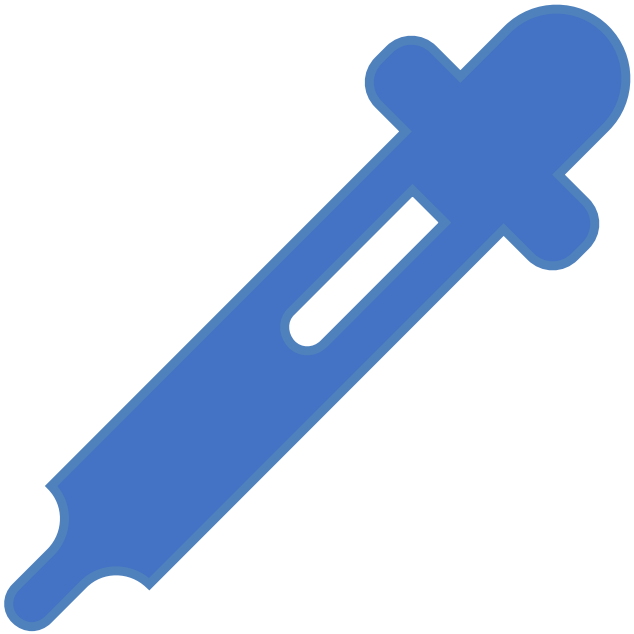
- Sensitivity of 91% and specificity of 94%
- Ultrasonography may be used as a screening test for HCC and portal hypertension
- Finding of nodules warrants further evaluation, since benign and malignant nodules can have similar ultrasonographic appearances.



CT and MRI???

Provide similar information as US at the expense of radiation and contrast exposure

MRI may reveal iron overload



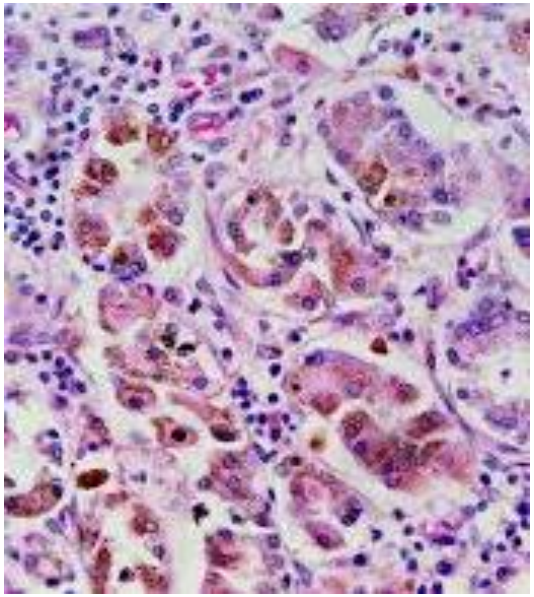
Liver Biopsy

The gold standard

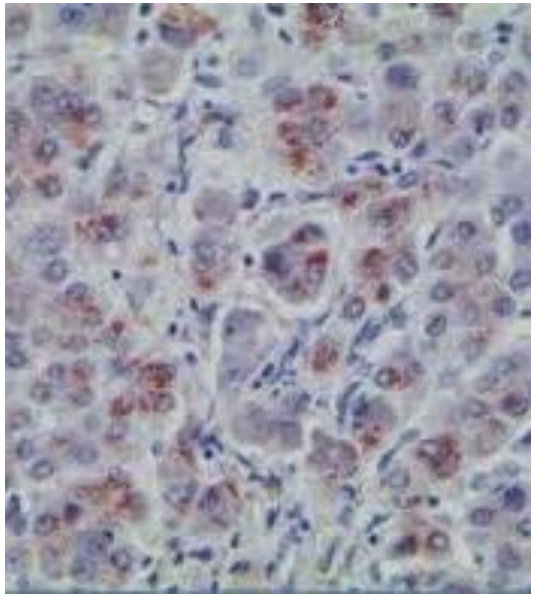
However, not necessary if:

- ❑ The clinical, laboratory, and radiologic data strongly suggest the presence of cirrhosis
- ❑ If the results would not alter the patient's management

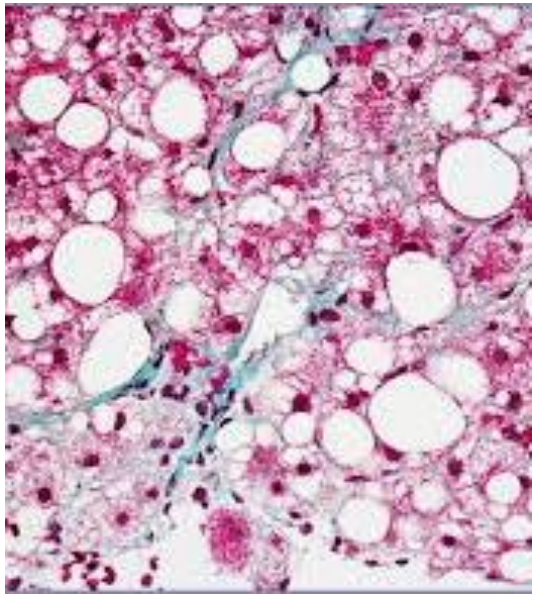
Solid liver masses	
Focal nodular hyperplasia	• Associated with anomalous arteries • Arterial flow & central scar on imaging
Hepatic adenoma	• Women on long-term oral contraceptives • Possible hemorrhage or malignant transformation
Regenerative nodules	• Acute or chronic liver injury (eg, cirrhosis)
Hepatocellular carcinoma	• Systemic symptoms • Chronic hepatitis or cirrhosis • Elevated alpha-fetoprotein
Liver metastasis	• Single/multiple lesions • Known extrahepatic malignancy



Hemochromatosis



Wilson disease



Fatty liver

Liver biopsy can sometimes suggest the cause

Additional Investigations

- **Hepatitis markers**
- **Hemochromatosis:** iron studies
- **Autoimmune hepatitis**: Gamma globulin, antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsomal antibodies
- **Wilson disease:** serum ceruloplasmin, evaluation for Kaiser-Fleisher rings
- **Alpha-1 antitrypsin deficiency:** serum alpha-1 antitrypsin level
- **Thyroid disorders:** TSH, free T4
- **Celiac disease:** serum tissue transglutaminase antibodies

Additional Investigations

- **Primary sclerosing cholangitis**
  - Antimitochondrial antibodies (AMA)
  - Antinuclear antibody
  - Antismooth muscle antibody

- **In case of cholestasis**
  - Endoscopic retrograde cholangiopancreatography(ERCP)
  - Magnetic resonance cholangiopancreatography (MRCP)
  - Computed tomography (CT)

Hepatitis Markers

Anti-HCV

❑ **If negative**

HCV infection is ruled out

❑ **If negative and no other etiology is apparent**

✓ Repeat anti-HCV test after 1-2 months

✓ Begins to become detectable 5-6 weeks after infection

❑ **If positive**

✓ Infection may be acute or chronic

✓ Active infection can be confirmed with a qualitative test for HCV-RNA

HBsAg

- **If negative**
  - ✓ HBV infection is ruled out with the rare exception of the "**window period**"
- **If positive**
  - ✓ Patient is infected with HBV and is infectious
- **If positive for longer than 6 months**
  - ✓ Chronic HBV infection

- **Once a chronic HBV diagnosis is made, testing for:**
  - ✓ HBeAg (active viral replication)
  - ✓ or HBV DNA (PCR)

All household and sexual contacts of a chronic HBV carrier should be investigated for HBV infection

Anti-HBsAB

❑ **If negative**

✓ no apparent immunity to HBV

❑ **If positive**

✓ Immune to HBV (either because of resolved infection or as a result of prior vaccination)

✓ These can be distinguished by testing for (anti-HBc-Total), which is present in subjects that have had HBV infection but absent in vaccines

Very rarely (<1%) chronic carriers can be positive for HBsAg and anti-HBs at the same time

Anti-HBc (IgG)

❑ **If negative**

✓ Past infection with HBV is ruled out

❑ **If positive**

✓ Patient has been infected with HBV

✓ Infection may be **resolved or ongoing**

✓ A negative HBsAg confirms a resolved infection

✓ If infection is resolved, the patient is considered **naturally immune to HBV infection**

Anti-HBc (IgM)

❑ **If negative**

Acute infection is ruled out

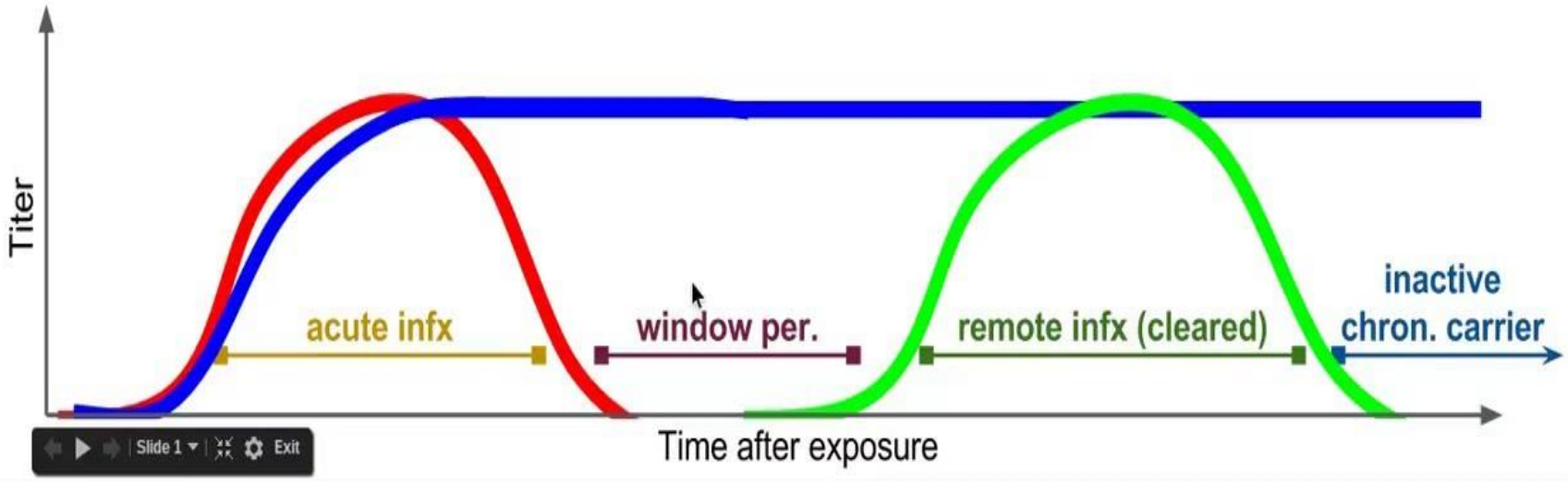
❑ **If positive**

✓ Assist in defining an acute infection

✓ Can be the only marker of infection present in '**window period**' when the HBsAg and anti-HBs tests are both undetectable.

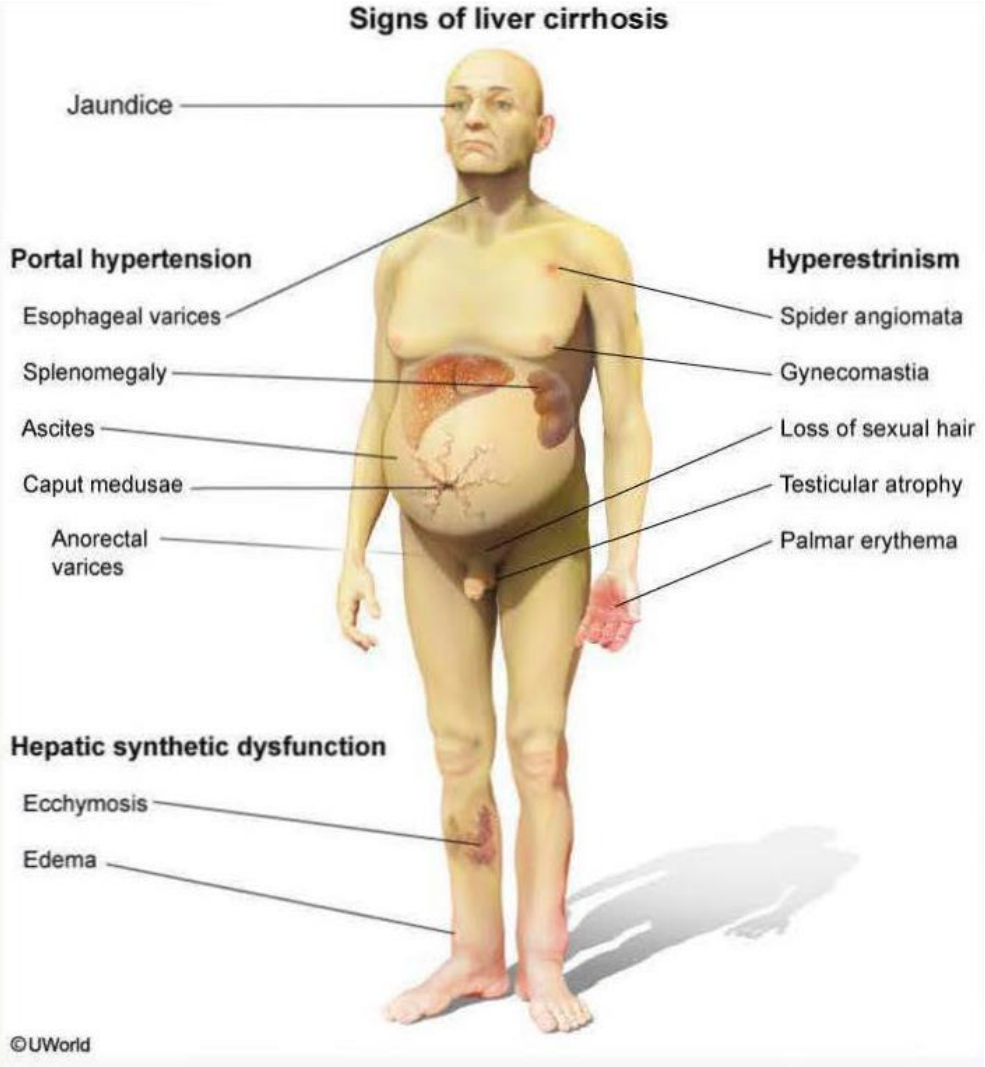
Hepatitis B serologies

Marker	Meaning	Acute infection	Window period	Chronic infection	Remote infection (cleared)	Immun-ization	Inactive chronic carrier
HBcAb	Exposure	+	+	+	+	-	+
HBsAg	Infection	+	-	+	-	-	-
HBsAb	Immunity	-	-	-	+	+	-



Red flags !! When to refer??

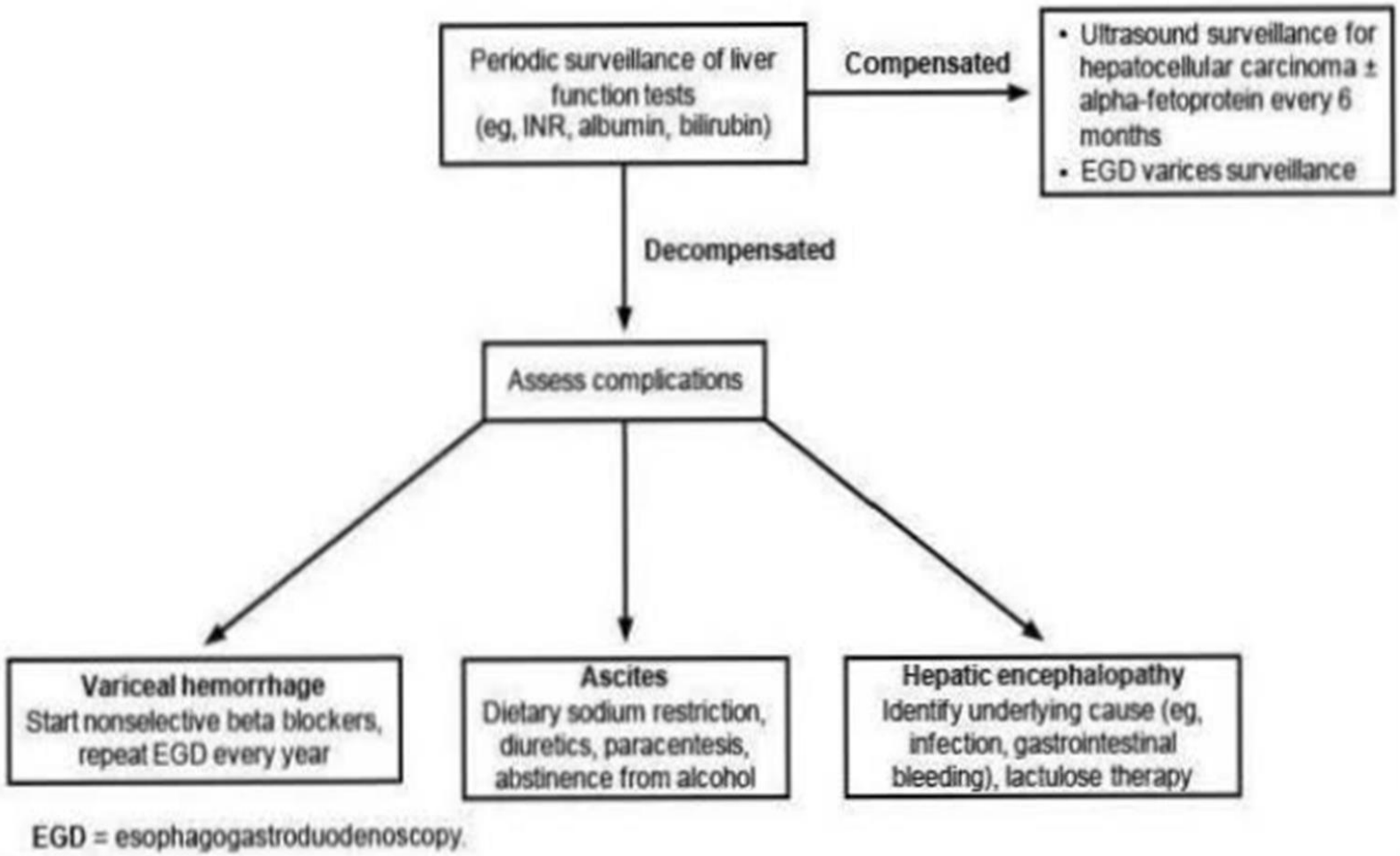
- Once these complications develop, patients are considered to have decompensated cirrhosis
- Once decompensation has developed, patients should be considered for liver transplantation



Factors that predispose to decompensation

- ❑Bleeding
- ❑Infection
- ❑Alcohol intake
- ❑Medications
- ❑Dehydration
- ❑Constipation
- ❑Obesity

Management of cirrhosis



EGD = esophagogastroduodenoscopy.

Ascites

- The most common complication of cirrhosis
- Due to portal hypertension
- Treated with diuretics and sodium restriction
- Repeated therapeutic paracentesis or TIPS placement

Ascites

Paracentesis should be performed if there is:

- New-onset ascites
- Abdominal pain and tenderness
- Fever

Portal hypertension from cirrhosis is the etiology of the ascitic fluid if there is a low albumin level in the fluid. The difference or "gradient" between the serum and ascites is also called the serum ascites albumin gradient (SAAG). If the SAAG is above 1.1, it is highly suggestive of portal hypertension.

SAAG: Correlating Level with Specific Diseases	
<1.1 g/dL	**>1.1 g/dL**
• Infections (except SBP) • Cancer • Nephrotic syndrome	• Portal hypertension • CHF • Hepatic vein thrombosis • Constrictive pericarditis

Common causes of ascites	
Extraperitoneal causes	• Cirrhosis • Acute liver failure • Alcoholic hepatitis • Budd-Chiari syndrome • Heart failure • Hypoalbuminemia • Malnutrition • Nephrotic syndrome
Peritoneal causes	• Malignancy (ovarian, pancreatic) • Infection (tuberculosis, fungal)

Ascites fluid characteristics	
Color	• **Bloody**: Trauma, malignancy, TB (rarely) • **Milky**: Chylous, pancreatic • **Turbid**: Possible infection • **Straw color**: Likely more benign causes
Neutrophils	• <250/mm^3: No peritonitis • ≥250/mm^3: Peritonitis (secondary or spontaneous bacterial)

Total protein	• ≥2.5 g/dL (high-protein ascites)
	  ○ CHF, constrictive pericarditis, peritoneal carcinomatosis, TB, Budd-Chiari syndrome, fungal (eg, coccidioidomycosis)
	• <2.5 g/dL (low-protein ascites)
	  ○ Cirrhosis, nephrotic syndrome

SAAG	• ≥1.1 g/dL (indicates portal hypertension)
	  ○ Cardiac ascites, cirrhosis, Budd-Chiari syndrome
	• <1.1 g/dL (absence of portal hypertension)
	  ○ TB, peritoneal carcinomatosis, pancreatic ascites, nephrotic syndrome

CHF = congestive heart failure; SAAG = serum-to-ascites albumin gradient; TB = tuberculosis.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is **infection without a perforation** of the bowel. We don't actually know how the bacteria gets there. *E coli* is the most common organism. Anaerobes are rarely the cause of SBP. Pneumococcus, a respiratory pathogen, causes SBP for unknown reasons.

Best initial test: **Cell count with more than 250 neutrophils** is the basis upon which we start therapy.

Gram stain is almost always negative. Fluid culture is the most accurate test, but the results are never available at the time we have to make a treatment decision.

LDH level is too nonspecific.

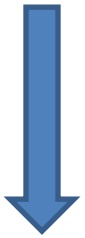
Treatment of SBP is with **cefotaxime or ceftriaxone**.

SBP frequently recurs. When the ascites fluid albumin level is quite low, prophylactic norfloxacin or trimethoprim/sulfamethoxazole is used to prevent SBP.

Spontaneous bacterial peritonitis	
Clinical presentation	• Temperature ≥37.8 C (100 F) • Abdominal pain/tenderness • Altered mental status (abnormal connect-the-numbers test) • Hypotension, hypothermia, paralytic ileus with severe infection
Diagnosis from ascitic fluid	• PMNs **≥250/mm^3** • Positive culture, often gram-negative organisms (eg, *Escherichia coli*, *Klebsiella*) • Protein <1 g/dL • SAAG ≥1.1 g/dL
Treatment	• Empiric antibiotics - third-generation cephalosporins (eg, cefotaxime) • Fluoroquinolones for SBP prophylaxis

PMN = polymorphonuclear leukocytes; **SAAG** = serum-ascites albumin gradient; **SBP** = spontaneous bacterial peritonitis.

Fever, Abdominal pain, Abdominal tenderness, and Altered mental status

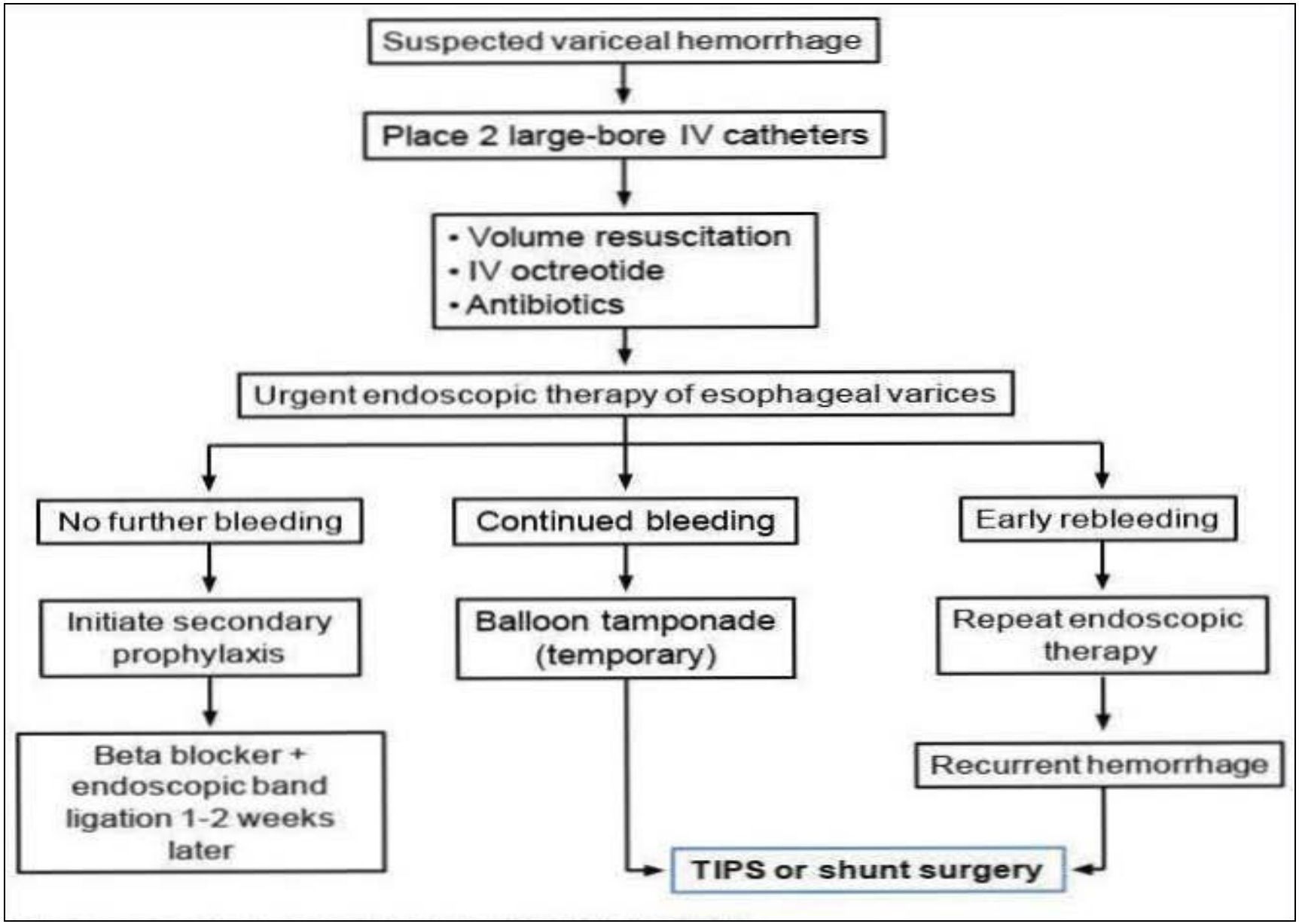


Spontaneous bacterial peritonitis (SBP)

The index of suspicion for SBP must be high

- ❑ Positive ascitic fluid bacterial culture and/or
- ❑ High ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3)

Without early antibiotic treatment, mortality is high


Suspected variceal hemorrhage
Place 2 large-bore IV catheters
• Volume resuscitation
• IV octreotide
• Antibiotics
Urgent endoscopic therapy of esophageal varices
No further bleeding
Continued bleeding
Early rebleeding
Initiate secondary prophylaxis
Balloon tamponade (temporary)
Repeat endoscopic therapy
Beta blocker + endoscopic band ligation 1-2 weeks later
Recurrent hemorrhage
TIPS or shunt surgery

Portal Hypertensive Gastropathy (Congestive Gastropathy)

- Extremely common in patients with portal hypertension and the severity of is related to the level of portal pressure

- Uncommon cause of significant bleeding

Disturbance in sleep patterns, Asterixis, Hyperactive deep tendon reflexes, Decerebrate Posturing

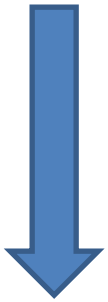
Hepatic encephalopathy

Hepatic encephalopathy

Precipitating factors	• Drugs (eg, sedatives, narcotics) • Hypovolemia (eg, diarrhea) • Electrolyte changes (eg, hypokalemia) • ↑ nitrogen load (eg, GI bleeding) • Infection (eg, pneumonia, UTI, SBP) • Portosystemic shunting (eg, TIPS)
Clinical presentation	• Sleep pattern changes • Altered mental status • Ataxia • Asterixis
Treatment	• Correct precipitating causes (eg, fluids, antibiotics) • ↓ blood ammonia concentration (eg, lactulose, rifaximin)

GI = gastrointestinal; **SBP** = spontaneous bacterial peritonitis; **TIPS** = transjugular intrahepatic portosystemic shunt; **UTI** = urinary tract infection.

Progressive rise in the plasma creatinine



Hepato-renal syndrome

The end-stage of a sequence of reductions in renal perfusion due to increasingly severe hepatic injury

Hepatopulmonary Syndrome

This is lung disease and hypoxia entirely on the basis of liver failure. Look for **orthodeoxia**, which is hypoxia upon sitting upright. There is no specific therapy.

Hepatocellular carcinoma (HCC)

Higher Risk

- HBV
- HCV
- Nonalcoholic steatohepatitis
- Hemochromatosis

Lower Risk

- Autoimmune hepatitis
- Wilson disease

Diagnosis of HCC

Clinical picture

- Frequently asymptomatic, the diagnosis is often delayed
- Decompensation in a patient with previously compensated cirrhosis
- **Mass effect:** pain, early satiety, obstructive jaundice, and a palpable mass

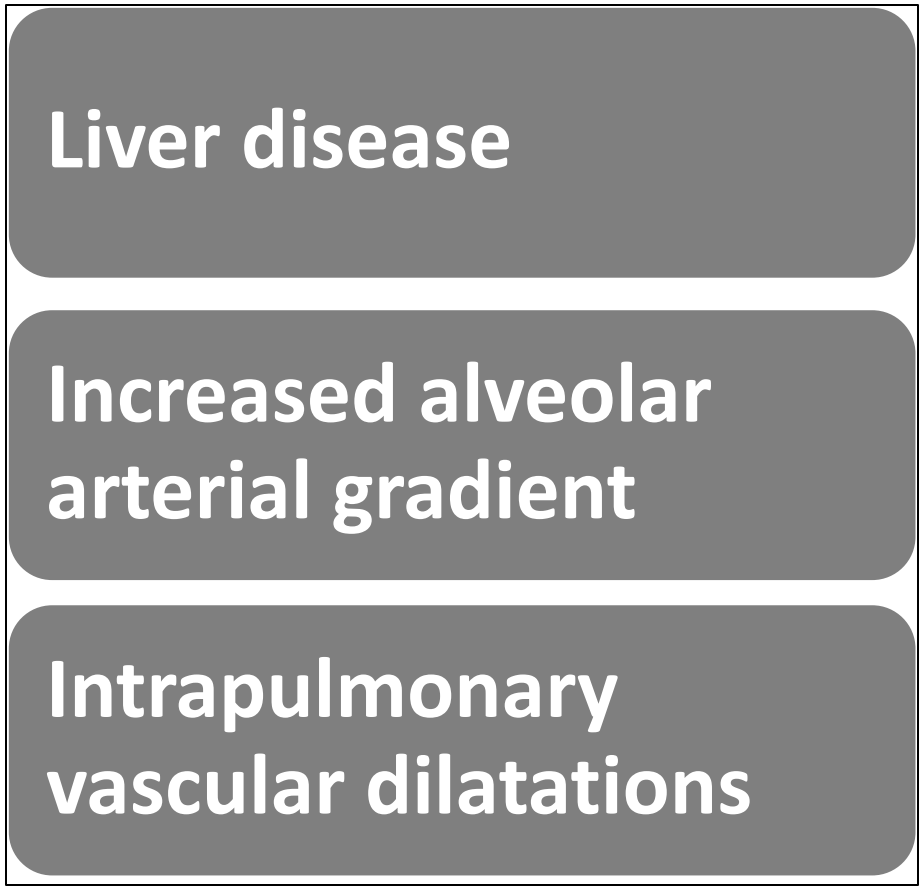
Alpha Feto Protein (AFP)

- Although nonspecific, rising serum AFP levels in a patient with cirrhosis should raise clinical suspicion for HCC
- However, a significant proportion of patients with HCC have normal AFP levels, especially when the tumor is small
- Normal AFP does not preclude a diagnosis

Cardiopulmonary complications

- **Hepatic hydrothorax:** movement of ascitic fluid into the pleural space through defects in the diaphragm

- Hepatopulmonary syndrome (HPS)

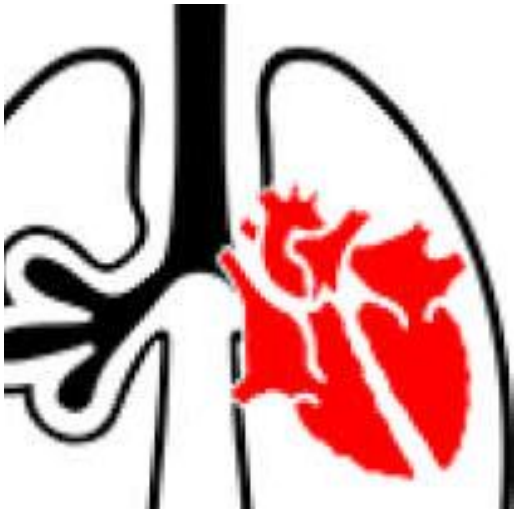


- **Porto-pulmonary hypertension**

The presence of pulmonary hypertension in patients with portal hypertension

- **Cirrhotic cardiomyopathy**

Up to 50% of patients with advanced cirrhosis have features of cardiac dysfunction especially with alcoholism or hemochromatosis



Acute liver failure	
Etiology	• Viral hepatitis (eg, HSV; CMV; hepatitis A, B, D & E) • Drug toxicity (eg, acetaminophen overdose, idiosyncratic) • Ischemia (eg, shock liver, Budd-Chiari syndrome) • Autoimmune hepatitis • Wilson disease • Malignant infiltration
Clinical presentation	• Generalized symptoms (eg, fatigue, lethargy, anorexia, nausea) • Right upper quadrant abdominal pain • Pruritus & jaundice due to hyperbilirubinemia • Renal insufficiency • Thrombocytopenia • Hypoglycemia
Diagnostic requirements	• Severe acute liver injury (ALT & AST often >1000 U/L) • Signs of hepatic encephalopathy (eg, confusion, asterixis) • Synthetic liver dysfunction (INR ≥1.5)

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **CMV** = cytomegalovirus; **HSV** = herpes simplex virus.

Treatment of Specific Features of Cirrhosis	
Feature	**Treatment**
Ascites and edema	Spironolactone and other diuretics. Serial paracenteses for large-volume ascites.
Coagulopathy and thrombocytopenia	FFP and/platelets only if bleeding occurs
Encephalopathy	Lactulose and rifaximin
Hypoalbuminemia	No specific therapy
Spider angiomata and palmar erythema	No specific therapy
Varices	Propranolol and banding via endoscopy
Hepatorenal syndrome	Somatostatin (octreotide), midodrine
Hepatopulmonary syndrome	No specific therapy

Child-Turcotte-Pugh Classification for Severity of Cirrhosis

Clinical and Lab Criterias	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3

***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**

Class A = 5 to 6 points (least severe liver disease)

Class B = 7 to 9 points (moderately severe liver disease)

Class C = 10 to 15 points (most severe liver disease)

Stages of Hepatic Encephalophay

Stage	Symptoms
I	Mild Confusion, agitation, irritability, sleep disturbance, decreased attention
II	Lethargy, disorientation, inappropriate behavior, drowsiness
III	Somnolent but arousable, slurred speech, confused, aggressive
IV	Coma

Specific Causes of Cirrhosis

Alcoholic Liver Disease

This is a diagnosis of exclusion. There is no specific therapy. The most accurate test, as with most of the causes of cirrhosis except for sclerosing cholangitis, is a liver biopsy.

Alcohol, like all drugs causing liver disease, gives a greater elevation in AST compared to ALT. Viral hepatitis gives a higher ALT than AST. Binge drinking gives a sudden rise in GGTP.

Clinical features of alcoholic hepatitis	
Clinical presentation	• Jaundice, anorexia, fever • Right upper quadrant &/or epigastric pain • Abdominal distension due to ascites • Proximal muscle weakness from muscle wasting (if malnourished) • Possible hepatic encephalopathy
Laboratory/ imaging studies	• Elevated AST & ALT, usually <300 U/L • AST:ALT ratio ≥2 • Elevated gamma-glutamyltransferase, bilirubin, &/or international normalized ratio • Leukocytosis, predominantly neutrophils • Decreased albumin if malnourished • Abdominal imaging may show fatty liver

Primary Biliary Cirrhosis

Answer primary biliary cirrhosis (PBC) as the "most likely diagnosis" when the question describes:

- Woman in 40s or 50s
- Fatigue and itching
- Normal bilirubin with an elevated alkaline phosphatase

Most unique features of PBC are:

- Xanthelasma/xanthoma
- Osteoporosis

Diagnostic Tests/Treatment

A liver biopsy is the most accurate test. The most accurate **blood** test is the **antimitochondrial antibody**. Bilirubin and IgM levels do not elevate until the disease is very far advanced. Treat PBC with **ursodeoxycholic acid**.

Primary biliary cholangitis	
Pathogenesis	• Autoimmune destruction of intrahepatic bile ducts
Clinical features	• Affects middle-age women • Insidious onset of **fatigue & pruritus** • Progressive jaundice, hepatomegaly, cirrhosis • Cutaneous **xanthomas & xanthelasmas**
Laboratory findings	• Cholestatic pattern of liver injury (↑↑ alkaline phosphatase, ↑ aminotransferases) • **Antimitochondrial antibody** • Severe hypercholesterolemia
Treatment	• **Ursodeoxycholic acid** (delays progression) • Liver transplantation for advanced disease
Complications	• Malabsorption, fat-soluble vitamin deficiencies • Metabolic bone disease (osteoporosis, osteomalacia) • Hepatocellular carcinoma

Primary Sclerosing Cholangitis

Over 80% of primary sclerosing cholangitis (PSC) occurs in association with inflammatory bowel disease. Look for:

PSC is the **only** cause of cirrhosis for which a biopsy is **not** the most accurate test.

- Pruritus
- Elevated alkaline phosphatase and GGTP as well as elevated bilirubin level

Early PSC can look just like PBC. The bilirubin level can be normal in early disease.

The most accurate test is an ERCP that shows beading, narrowing, or strictures in the biliary system. You can diagnose PSC from a biopsy if it was done for other reasons, but biopsy is not essential for establishing the diagnosis. Treat with cholestyramine or ursodeoxycholic acid, the same as PBC.

▶ TIP

PSC does not improve or resolve with resolution of the IBD. Even after a colectomy in ulcerative colitis, the patient may still progress to needing a liver transplantation.

Acute cholangitis	
Clinical presentation	• Fever, jaundice, right upper quadrant pain (Charcot triad) • Mental status changes, hypotension (Reynolds pentad) • Liver failure • Acute kidney injury
Diagnosis	• Biliary dilation on ultrasound or CT scan • ↑ Alkaline phosphatase, gamma-glutamyl transpeptidase, direct bilirubin • Leukocytosis, ↑ C-reactive protein
Treatment	• Biliary drainage: Endoscopic retrograde cholangiopancreatography with sphincterotomy or percutaneous transhepatic cholangiography • Broad-spectrum antibiotics: Beta-lactam/beta-lactamase inhibitor, third-generation cephalosporin + metronidazole

Alpha 1-Antitrypsin Deficiency

Look for the combination of **liver disease** and **emphysema (COPD)** in a **young patient** (under 40) who is a **nonsmoker**. They may throw in a family history of COPD at an early age. Treat by replacing the enzyme. The most frequently asked question is "What is the most likely diagnosis?"

Hemochromatosis

This is a genetic disorder leading to **overabsorption of iron in the duodenum**. The mutation is the C282y gene.

Men present earlier than women because **menstruation delays the onset** of liver fibrosis and cirrhosis.

Presentation

Look for a patient in his 50s with mild increases in AST and alkaline phosphatase and:

- Fatigue and joint pain (pseudogout)
- Erectile dysfunction in men, and amenorrhea in women (from pituitary involvement)
- Skin darkening

- Diabetes
- Cardiomyopathy

Hemochromatosis **may be found on routine testing** with mildly abnormal liver function tests (LFTs) or iron levels.

Diagnostic Tests

The best initial test is iron studies that show:

- Increased serum iron and ferritin
- Decreased iron binding capacity

The most accurate test is a liver biopsy for increased iron. The EKG may show conduction defects and the echocardiogram can show dilated or restrictive cardiomyopathy.

Treatment

Phlebotomy is clearly the best therapy for those with overabsorption of iron.

Liver fibrosis can resolve if phlebotomy is begun before cirrhosis develops.

Vibrio vulnificus, *Yersina*, and *Listeria* infections occur because these organisms feed on iron.

A 54-year-old man has been evaluated in the office for fatigue, erectile dysfunction, and skin darkening. He is found to have transferrin saturation (iron divided by TIBC) above 50%. His AST is 2 times the upper limit of normal.

What would you do next to confirm the diagnosis?

a. Echocardiography
b. Glucose level
c. Abdominal MRI and HFE (C282y) gene testing
d. Liver biopsy
e. Prussian blue stain of the bone marrow
f. Deferoxamine
g. Deferasirox

Answer: C. MRI will show increased iron deposition in the liver. An abnormal MRI combined with an abnormal genetic test for hemochromatosis can spare the patient the need for a liver biopsy. There is an association with diabetes; however, glucose levels will not confirm a diagnosis of hemochromatosis. Prussian blue is the stain of blood cells for iron. Prussian blue is also used to diagnose sideroblastic anemia.

Iron chelation therapy is used in hemochromatosis for those who:

1. *Cannot be managed with phlebotomy*
2. *Are anemic and have hemochromatosis from overtransfusion such as thalassemia*

Deferoxamine, deferasirox, or deferiprone should not be started until the diagnosis is confirmed. Deferasirox and deferiprone are huge breakthrough medications because they are effective orally. Deferoxamine has to be given lifelong by injection.

Wilson Disease

This is a disorder of abnormally decreased copper excretion from the body. Because of a decrease in ceruloplasmin, copper is not excreted and it builds up in the body in the liver, kidney, red blood cells, and the nervous system.

"What Is the Most Likely Diagnosis?"

In addition to all the previously described features of cirrhosis and hepatic insufficiency, you will answer Wilson disease as the diagnosis if you see:

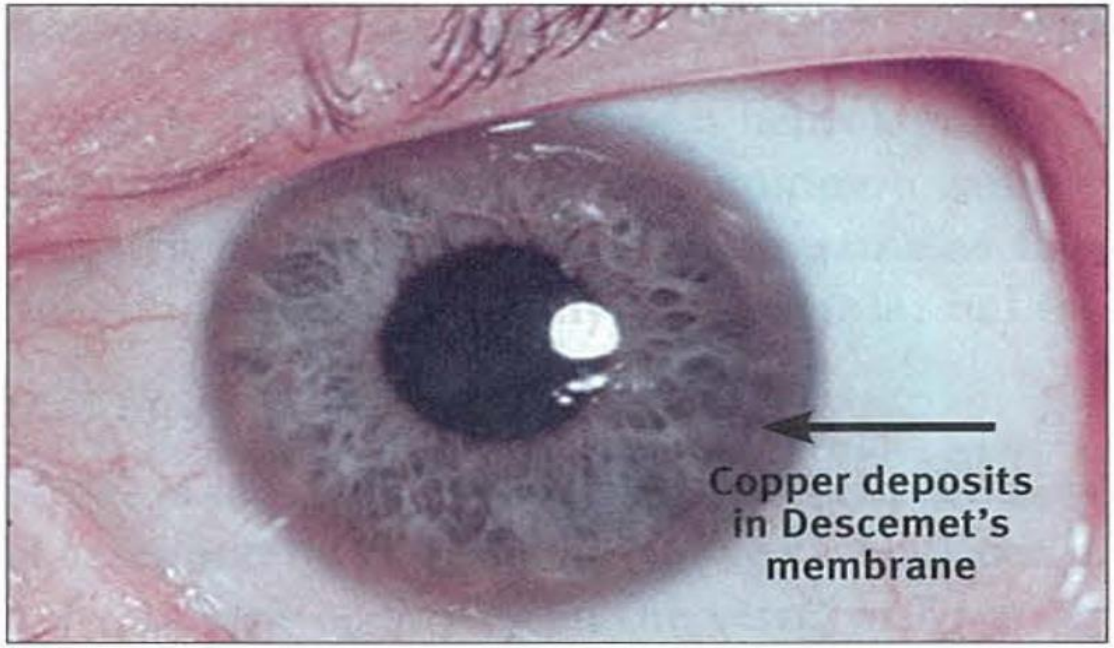
- Neurological symptoms: psychosis, tremor, dysarthria, ataxia, or seizures
- **Coombs negative hemolytic anemia**
- Renal tubular acidosis or nephrolithiasis

▶ TIP

Wilson disease gives psychosis and delusions—not the encephalopathic features or delirium that you would get with any form of liver failure.

Diagnostic Tests

The best initial test is a **slit-lamp** examination for **Kayser-Fleischer rings**, a brownish ring around the eye from copper deposition. Ceruloplasmin is usually low. Liver biopsy is more sensitive and specific and will detect abnormally increased hepatic copper.



Decreased ceruloplasmin level is not the most accurate test. This is the most common wrong answer. All plasma proteins can be decreased in those with liver dysfunction and cirrhosis.

Figure 8.6: Copper deposits in the Descemet membrane give a brownish ring around the outer edge of the cornea. *Source: Herbert L. Fred, MD, Hendrik A. van Dijk.*

The most accurate diagnostic test is looking at an abnormally increased amount of copper excretion into the urine after giving penicillamine.

Treatment

Penicillamine will chelate copper and remove it from the body. Additional therapies are:

- **Zinc: interferes with intestinal copper absorption**
- Trientine: an alternate copper-chelating compound

Autoimmune Hepatitis

Look for a **young woman with other autoimmune diseases**, such as Coombs positive hemolytic anemia, thyroiditis, and ITP.

Diagnostic Testing

- Best initial tests: **ANA and antismooth muscle antibody test. Serum protein electrophoresis** (SPEP) shows hypergammaglobulinemia. The patient may also have positive ANA and liver/kidney microsomal antibody.
- Most accurate test: **Liver biopsy**

Treatment

Treat with **prednisone.** Other immunosuppressive agents, such as azathioprine, may be needed if one is attempting to wean the patient off steroids.

Nonalcoholic Steatohepatitis (NASH) or Nonalcoholic Fatty Liver Disease

Nonalcoholic steatohepatitis is an extremely common cause of mildly abnormal liver function tests. The biopsy is the most accurate test and shows the microvesicular fatty deposits you would find in alcoholic liver disease, but without the history of alcohol use.

This disorder is associated with:

- Obesity
- Diabetes
- Hyperlipidemia
- Corticosteroid use

The most important issue is to exclude more serious liver disease. Management is with correcting the underlying causes previously described. There is no specific drug therapy to reverse it.

Nonalcoholic fatty liver disease	
Definition	• Hepatic steatosis on imaging or biopsy • Exclusion of significant alcohol use • Exclusion of other causes of fatty liver
Clinical features	• Mostly asymptomatic • Metabolic syndrome • +/- Steatohepatitis (AST/ALT ratio <1) • Hyperechoic texture on ultrasound
Treatment	• Diet & exercise • Consider bariatric surgery if BMI ≥35

AST = aspartate aminotransferase; **ALT** = alanine aminotransferase.

Hepatitis

Patients with **acute hepatitis** will all present is a very similar way. You *cannot* accurately determine the etiology of acute hepatitis from history and presentation alone. All patients present with:

- **Jaundice**
- **Fatigue**
- **Weight loss**
- **Dark urine caused by bilirubin in the urine**

- Hepatitis B is associated with polyarteritis nodosa (PAN) in 30 percent of cases.
- Hepatitis C is associated with cryoglobulinemia.

Hepatitis B and C are more likely to present with **serum sickness-phenomena** like joint pain, urticaria, and fever.

Hepatitis E is most severe in pregnant women. It can be fatal.

- Viral: ↑ ALT
- Drugs: ↑ AST

Diagnostic Testing

All patients with acute hepatitis will give an **elevated conjugated (direct) bilirubin.** This will lead to bilirubin in the urine or urobilinogen. Uncon-jugated bilirubin, such as that associated with hemolysis, is not water soluble and will not pass into the urine. Unconjugated bilirubin is attached to albumin.

- **Viral hepatitis** gives an **elevated ALT level.**
- **Drug-induced hepatitis** is associated with an **increased AST.**

Most accurate tests:

- For **hepatitis A, C, D, and E**, the confirmatory test is **serology.** IgM levels acutely rise, and IgG levels rise in the recovery phase.
- **Surface antigen, core antibody, e-antigen, or surface antibodies** are not present in hepatitis A, C, D, or E. These tests are associated with **hepatitis B.**

Acute Hepatitis B

The *first* test to become abnormal in acute hepatitis B infection is the **surface antigen.** Elevation in ALT, e-antigen, and symptoms all occur *after* the appearance of hepatitis B surface antigen. The following table shows the appearance of the antigens and antibodies through the course of the disease:

	Surface Antigen	e-Antigen	Core Antibody	Surface Antibody
Acute disease (hepatitis B)	+ +	+ +	+ +	–
Window period (recovering)	–	–	+ +	–
Vaccinated	–	–	–	+ +
Healed/recovered	–	–	+ +	+ +

Chronic hepatitis B gives the same serologic pattern as acute hepatitis B, but it is based on **persistence of the surface antigen beyond 6 months.**

	Surface Antigen	e-Antigen	Core Antibody	Surface Antibody
Acute hepatitis B	+	+	+	–
Chronic hepatitis B	+	+	+	–
Resolved infection	–	–	+	+
Window period	–	–	+	–

These 3 tests are essentially *equal* in meaning. They all indicate **active viral replication:**

Hepatitis B DNA polymerase = e-Antigen = Hepatitis B PCR for DNA

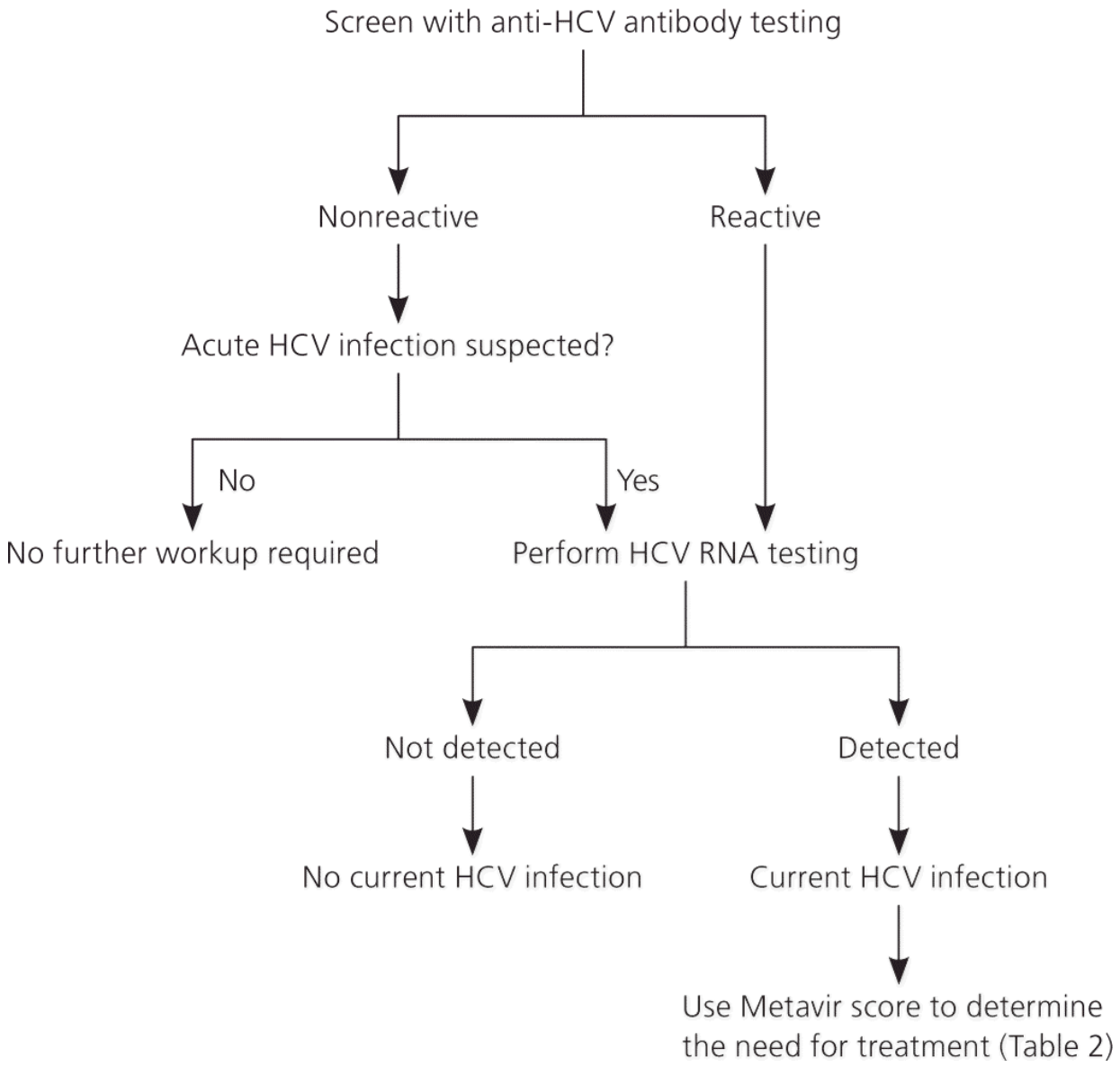
No treatment is available for acute hepatitis B.

Acute Hepatitis C

- Best initial test: **Hepatitis C antibody.** This test *cannot*, however, tell the level of activity of the virus.
- Most accurate tests:
  - **Hepatitis C PCR** for RNA is the most accurate method of determining the degree of viral replication and activity of the disease. PCR RNA is also the most accurate way of determining response to therapy.
  - **Liver biopsy** is the most accurate way of determining the seriousness of the disease. The patient can have 10 years of active viral replication with relatively little liver damage. Use the biopsy to determine extent of damage to the liver.

Acute hepatitis C is treated with interferon/ribavirin and an oral protease inhibitor, the same as chronic disease.

The only acute hepatitis that can be treated is acute hepatitis C.


Screen with anti-HCV antibody testing
Nonreactive
Reactive
Acute HCV infection suspected?
No
Yes
No further workup required
Perform HCV RNA testing
Not detected
Detected
No current HCV infection
Current HCV infection
Use Metavir score to determine
the need for treatment (Table 2)

Diagnosis of Acute HCV

Recommended Testing for Diagnosing Acute HCV Infection	
RECOMMENDED	RATING ⓘ
HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Testing Algorithm figure).	I, C

TEST	INTERPRETATION FOR DIAGNOSIS OF ACUTE HCV
HCV Antibody	• Test may be negative during the first 6 weeks after exposure. • Seroconversion may be delayed or absent in immunosuppressed individuals. • Presence of HCV antibody alone does not distinguish between acute vs chronic infection.
HCV RNA	• Viral fluctuations >1 $\log_{10}$ IU/mL may indicate acute HCV infection. • HCV RNA may be transiently negative during acute HCV infection. • Presence of HCV RNA alone does not distinguish between acute vs chronic infection.
ALT	• Fluctuating ALT peaks suggest acute infection. • ALT may be normal during acute HCV infection. • ALT may be elevated due to other liver insults, such as alcohol consumption.

Pharmacologic Prophylaxis

Pharmacologic Prophylaxis Not Recommended	
NOT RECOMMENDED	RATING
Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.	III, C

There are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection.

Medical Management and Monitoring of Acute HCV Infection

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING
After the initial diagnosis of acute HCV with viremia (defined as quantifiable RNA), HCV treatment should be initiated without awaiting spontaneous resolution.	I, B
Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

Antiviral Therapy

Recommended Regimens for Patients With Acute HCV Infection	
RECOMMENDED	RATING ⓘ
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

Clinical features of chronic hepatitis C

Clinical presentation	• Can be asymptomatic or develop fatigue (most common) • Other nonspecific symptoms (eg, nausea, anorexia, myalgia, arthralgia, weakness, weight loss) • Serum **transaminases** can be elevated or **normal** (up to 1/3 of patients) • Can progress to cirrhosis in up to 20% of patients • Increased risk of hepatocellular carcinoma
Extrahepatic manifestations	• Heme: Essential mixed cryoglobulinemia • Renal: Membranoproliferative glomerulonephritis • Skin: Porphyria cutanea tarda, lichen planus • Endocrine: Increased risk of diabetes

Chronic Hepatitis B

The patient with surface antigen, e-antigen, and DNA polymerase or PCR for DNA is the patient who is most likely to benefit from **antiviral therapy.** Look for **> 6 months of positive serology.**

Chronic hepatitis B is treated with one of the following single agents:

- **Lamivudine**
- **Adefovir**
- **Entecavir**
- **Telbivudine**
- **Tenofovir**
- **Interferon:** Interferon has the most adverse effects:
  - Flulike symptoms
  - Arthralgia
  - Myalgia
  - Fatigue
  - Thrombocytopenia
  - Depression

Chronic Hepatitis C

Treat with **interferon combined with ribavirin and boceprevir or telaprevir.** The most common adverse effect of ribavirin is **anemia.**

- Oral protease inhibitors such as **simeprevir or sofosbuvir** are added to ribavirin and interferon or can be used without interferon. The only form of acute hepatitis that receives antiviral therapy is acute hepatitis C. Telaprevir, simeprevir, and boceprevir are considered interchangeable.
- Chronic hepatitis C is the most common reason to need a liver transplantation in the United States.

Add boceprevir, telaprevir, or simeprevir to hepatitis C treatment.

Sofosbuvir allows treatment without interferon for hepatitis C.

Criteria for TTT

Antiviral therapy for chronic hepatitis C should be determined on a case-by-case basis.

However, treatment is widely recommended for patients with elevated serum alanine aminotransferase (ALT) levels who meet the following criteria:

- ❑ Age older than 18 years
- ❑ Positive HCV antibody and serum HCV RNA test results
- ❑ Compensated liver disease (e.g., no hepatic encephalopathy or ascites)
- ❑ Acceptable hematologic and biochemical indices (hemoglobin at least 13 g/dL for men and 12 g/dL for women; neutrophil count >1500/mm 3, serum creatinine < 1.5 mg/dL)
- ❑ Willingness to be treated and to adhere to treatment requirements
- ❑ No contraindications for treatment

Table 2. Metavir Scoring System for the Assessment of Liver Fibrosis and Cirrhosis

Level of fibrosis	*Score*
No fibrosis	0
Minimal scarring	1
Positive scarring with extension beyond area containing blood vessels	2
Bridging fibrosis with connection to other areas of fibrosis	3
Cirrhosis or advanced liver scarring	4

NOTE: *Treatment should be considered in patients with a score ≥ 2.*[6]

Information from references 6 and 18.

Table 3. Predictors of SVR in Treatment of HCV Infection

Factor	*Comment*
Age	Rates of SVR are higher in patients younger than 40 to 45 years[25]
Fibrosis	Advanced fibrosis and cirrhosis are associated with lower SVR[25]
Hepatitis C genotype	Strongest baseline predictor for SVR; SVR is highest for genotypes 2 and 3 and lowest for genotype 1[26]
IL28B polymorphisms	*IL28B* gene is involved in viral resistance and is upregulated by interferons; genotypes CC and TT are strong SVR predictors for HCV genotype 1; TT is associated with slightly increased SVR in Asians with genotypes 2 and 3[27]
Insulin resistance	Patients with normal insulin sensitivity have higher SVR compared with patients with insulin resistance (odds ratio = 2.86)[28]
Lower baseline viral load	≤ 600,000 to 800,000 IU per mL is associated with higher SVR[25,29]
Race	Blacks have lower SVR rates than nonblacks[25]
Statin use	Patients treated with statins have higher SVR compared with patients not treated with statins[30,31]

HCV = hepatitis C virus; SVR = sustained viral response.

Information from references 25 through 31.

Criteria of TTT

Treatment is recommended for adults with chronic hepatitis B infection without clinical evidence of cirrhosis but who have all of the following features, and regardless of HBeAg status (strong recommendation):

- Are older than 30 years (in particular)
- Have persistently abnormal ALT levels
- Have evidence of high-level HBV replication (HBV DNA >20,000 IU/mL).

(If HBV DNA testing is unavailable, consider treatment based on persistently abnormal ALT levels alone, regardless of HBeAg status.

Overview of hepatitis B virus treatment

Patients to treat	• Acute liver failure • Clinical complications of cirrhosis • Advanced cirrhosis with high serum HBV DNA • Patients without cirrhosis but with positive HBeAg, HBV DNA >20,000 IU/mL & serum ALT >2x upper limit of normal • Prevent HBV reactivation during chemotherapy or immunosuppression
Available treatments	• **Interferon**: Usually for younger patients with compensated liver disease; short-term treatment • **Lamivudine**: Diminished role due to higher drug resistance; may have role in HIV patients • **Entecavir**: Can be used in decompensated cirrhosis; lower rate of drug resistance than lamivudine • **Tenofovir**: Most potent with limited drug resistance; preferred drug (in countries that have approved it)

Vaccination

Vaccination for both **hepatitis A and B** is now done universally in **childhood.**

For **adults,** the strongest indications for vaccination for both **hepatitis A and B** are the following:

- **Chronic liver disease.** Someone with cirrhosis or another cause of liver disease who develops hepatitis A or B is at *much* greater risk of fulminant hepatitis.
- **Household contacts** of those with hepatitis A or B
- **Men who have sex with men**
- **Chronic recipients of blood products**
- **Injection drug users**

Specific indications for vaccines are as follows:

- **Hepatitis A vaccine**
  - Travelers
- **Hepatitis B vaccine**
  - Health care workers
  - Patients on dialysis
  - Diabetes

A health care worker gets stuck with a needle contaminated with blood from a person with chronic hepatitis B. The health care worker has never been vaccinated. What is the most appropriate action?

Answer: Give hepatitis B immune globulin and hepatitis B vaccine. The same recommendation would be made for a child born to a mother with chronic hepatitis B. If the person had already been vaccinated, then you would check for levels of protective surface antibody. If hepatitis B surface antibody were already present, then no further treatment would be necessary.

There is *no* vaccine and *no* postexposure prophylaxis for **hepatitis C.**

Recommended vaccines for chronic liver disease	
Tdap/Td	Tdap once as substitute for Td booster, then Td every 10 years
Influenza	Annually
Pneumococcal vaccines	PPSV23 once, then revaccination with sequential PCV13 & PPSV23 at age 65
Hepatitis A	2 doses 6 months apart with initial negative serologies
Hepatitis B	3 doses at 0 months, 1 month & at least 4 months with initial negative serologies

PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; Td = tetanus-diphtheria toxoid booster; Tdap = tetanus-diphtheria-acellular pertussis.

Hepatitis C in pregnancy	
Potential complications	• Gestational diabetes • Cholestasis of pregnancy • Preterm delivery
Maternal management	• Ribavirin is **teratogenic** & should be avoided • No indication for barrier protection in serodiscordant, monogamous couples • Hepatitis A & B vaccination
Prevention of vertical transmission	• Vertical transmission strongly associated with maternal viral load • Cesarean delivery not protective • Scalp electrodes should be avoided • Breastfeeding should be encouraged unless maternal blood present (eg, nipple injury)